third edition

DEVELOPMENTAL PSYCHOPATHOLOGY

VOLUME 3

MALADAPTATION AND PSYCHOPATHOLOGY

EDITED BY **Dante Cicchetti**

DEVELOPMENTAL PSYCHOPATHOLOGY

DEVELOPMENTAL PSYCHOPATHOLOGY

THIRD EDITION

Volume Three: Maladaptation and Psychopathology

Editor

DANTE CICCHETTI

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of her great vision and staunch support of the field
of developmental psychopathology.

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Preface to Developmental Psychopathology, Third Edition

A decade has passed since the second edition of *Developmental Psychopathology* was published. The two prior editions (Cicchetti & Cohen, 1995, 2006) have been very influential in the growth of the field of developmental psychopathology. The volumes have been highly cited in the literature and have served as an important resource for developmental scientists and prevention and intervention researchers alike. In the present third edition, we have expanded from the three volumes contained in the second edition to four volumes. The increased number of volumes in this current edition reflects the continued knowledge gains that have occurred in the field over the past decade.

A not insignificant contributor to this growth can be found in the very principles of the discipline (Cicchetti, 1984, 1990, 1993; Cicchetti & Sroufe, 2000; Cicchetti & Toth, 1991, 2009; Rutter & Sroufe, 2000; Sroufe & Rutter, 1984). Theorists, researchers, and prevention scientists in the field of developmental psychopathology adhere to a life span framework to elucidate the numerous processes and mechanisms that can contribute to the development of mental disorders in high-risk individuals as well as those operative in individuals who already have manifested psychological disturbances or who have averted such disorders despite their high-risk status (Cicchetti, 1993; Masten, 2014; Rutter, 1986, 1987, 2012). Not only is knowledge of normal genetic, neurobiological, physiological, hormonal, psychological, and social processes very helpful for understanding, preventing, and treating psychopathology, but also deviations from and distortions of normal development that are seen in pathological processes indicate in innovative ways how normal development may be better investigated and understood. Similarly, information obtained from investigations of experiments of nature, high-risk conditions, and psychopathology can augment the comprehension of normal development (Cicchetti, 1984, 1990, 1993; Rutter, 1986; Rutter & Garmezy, 1983; Sroufe, 1990; Weiss, 1969).

Another factor that has expedited growth within the field of developmental psychopathology has been its ability to incorporate knowledge from diverse disciplines and to encourage interdisciplinary and translational research (Cicchetti & Gunnar, 2009; Cicchetti & Toth, 2006). In keeping with its integrative focus, contributions to developmental psychopathology have come from many disciplines of the biological and social sciences. A wide array of content areas, scientific disciplines, and methodologies has been germane. Risk and protective factors and processes have been identified and validated at multiple levels of analysis and in multiple domains.

The increased emphasis on a multilevel, dynamic systems approach to psychopathology and resilience, the increased attention paid to gene–environment interplay in the development of psychopathology and resilience, and the application of a multiple levels of analysis developmental perspective to mental illnesses that have traditionally been examined nondevelopmentally (e.g., bipolar disorder, schizophrenia, and the personality disorders) not only have contributed to a deeper understanding of the dysfunctions but also have educated the public about the causes and consequences of mental disorder (see Cicchetti & Cannon, 1999; Cicchetti & Crick, 2009a, 2009b; Miklowitz & Cicchetti, 2006, 2010; Tackett & Sharp, 2014).

Advances in genomics, GxE interactions, and epigenetics; growth in our understanding of neurobiology, neural plasticity, and resilience; and progress in the development of methodological and technological tools, including brain imaging, neural circuitry, hormone assays, immunology, social and environmental influences on brain development, and statistical analysis of developmental change, pave the way for interdisciplinary and for multiple levels of analysis research programs that will significantly increase the knowledge base of the development and course of maladaptation, psychopathology, and resilience. Moreover, randomized control prevention and intervention trials are being conducted based on theoretical models and efforts to elucidate the mechanisms and processes contributing to developmental change at both the biological and psychological levels (Belsky & van IJzendoorn, 2015; Cicchetti & Gunnar, 2008).

Despite the significant advances that have occurred in the field of developmental psychopathology, much important work lies ahead. Undoubtedly these future developments will build on the venerable contributions of the past; however, as work in the field becomes increasingly interdisciplinary, multilevel, and technologically sophisticated, it is essential that even more emphasis be directed toward the process of development (Harter, 2006; Sroufe, 2007, 2013). It is not only genes and environments but also the cumulative developmental history of the individual that influences how future development will unfold (Sroufe, 2007, 2013).

Developmental psychopathologists have incorporated concepts and methods derived from other disciplinary endeavors that are too often isolated from each other, thereby generating advances in knowledge that might have been missed in the absence of cross-disciplinary dialogue. The continuation and elaboration of the mutually enriching interchanges that have occurred within and across disciplines interested in normal and abnormal development not only will enhance the science of developmental psychopathology but also will increase the benefits to be derived for individuals with high-risk conditions or mental disorders, families, and society as a whole.

Dante Cicchetti, Ph.D.
Minneapolis, MN
January 2015

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DEVELOPMENTAL PSYCHOPATHOLOGY

CHAPTER 1

Developments in the Developmental Approach to Intellectual Disability

JACOB A. BURACK, NATALIE RUSSO, CATHRYN GORDON GREEN, ORIANE LANDRY, and GRACE IAROCCI

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DEVELOPMENTS IN THE DEVELOPMENTAL APPROACH TO INTELLECTUAL DISABILITY

The developmental study of intellectual disability is a long-established forerunner of developmental psychopathology with origins that predate the formal emergence of the latter discipline by decades, and yet is still in its early, and sometimes apparently regressive, stages of developmental emergence relative to other areas of work. It was largely shaped by scholars, such as Heinz Werner, Edward Zigler, and Dante Cicchetti, who were also seminal to the emergence of the scholarly discipline of developmental psychopathology, and yet it is often conceptualized as a separate unrelated entity. These complex relationships provide a lens through which we can understand the advances, and setbacks, in the study of intellectual disability, and its place in the domain of developmental psychopathology

"Make for yourself a teacher, acquire for yourself a friend, and judge everyone in a positive light . . . " Ethics of the Fathers (Pirkei Avot, 1, 6). We dedicate this chapter in honor of Ed Zigler for all his contributions to the science and welfare of so many children, including those with intellectual disability. He is the most inspiring teacher, loyal friend, and positive influence to all who know him. As with so much of his work, his articulation of the developmental approach to intellectual disability helped humanize our understanding of a population that for too long had been underserved and kept at the fringes of society. We are especially grateful to Dante Cicchetti for inviting us to contribute this chapter, on a topic about which we are so passionate and about which he was a visionary. His leadership both in the world of science and in making the world a better place for children is an example to us all.

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(and thereby in this volume). Within this framework, we highlight the thinking and research that led to and continue to maintain the developmental approach to intellectual disability and consider them with regard to developments in the study and understanding of intellectual disability since Hodapp and Burack's (2006) chapter in the last edition of this handbook (Cicchetti & Cohen, 2006).

As intellectual disability is essentially defined by the development of cognitive abilities and, to a considerably lesser extent, social skills that are so delayed and ultimately impaired that it only involves a small percentage of persons, it is a paradigmatic example of the construct of development at the extreme that is so essential to the field of developmental psychopathology (Burack, 1997; Cicchetti & Pogge-Hesse, 1982). In this way, intellectual disability also exemplifies Urie Bronfenbrenner's notion of an experiment of nature, which could never be replicated in an experimental setting but in this case is informative for understanding the course of typical cognitive and social development. Thus, consistent with Cicchetti's (1984) dictum that "you can learn more about typical functioning by studying its pathology and more about its pathology by studying its typical state" (p. 4), intellectual disability is a window into addressing issues and questions about cognitive and social development that cannot be fully answered when only considering typically developing persons (Burack, 1997; Cicchetti & Pogge-Hese, 1982; Hodapp, Burack, & Zigler, 1990). In providing the example of extreme delay, or impairment, intellectual disability would appear to allow us the opportunity to examine the integrity of the developmental system from the unique perspective of especially slowed or delayed development (Cicchetti & Beegly, 1990; Hodapp & Burack, 1990; Hodapp & Zigler, 1990). As is often the case in nature, this "slow motion" analysis of cognitive and social development allows for a particularly intense level of scrutiny that cannot be attained with events occurring at their typical speed.

The converse of Cicchetti's dictum is also particularly relevant to the study of intellectual disability as the theories and methodologies that have governed the study of development among typically developing persons have, during the past half century, transformed the way that persons with intellectual disability and their families are studied, understood, educated, and supported (for related collections, see Burack, Hodapp, Iarocci, & Zigler, 2012; Burack, Hodapp, & Zigler, 1998; Cicchetti & Beeghly, 1990; Hodapp, Burack, & Zigler, 1990). These advances are the focus of this chapter as we highlight the ongoing and evolving conceptual, methodological, and interpretive contributions of the so-called developmental approach to the study of persons with intellectual disability and the ways that they have led to a more precise and sophisticated science (Burack, Dawkins, Stewart, Flores, Iarocci, & Russo, 2012; Burack, Russo, Flores, Iarocci, & Zigler, 2012; Cicchetti & Ganiban, 1990; Hodapp, Burack, & Zigler; 1990).

THE DIAGNOSIS OF INTELLECTUAL DISABILITY AND ITS (LACK OF) MEANINGFULNESS

Although the diagnosis has far-reaching implications for the development and outcomes of the affected persons, intellectual disability cannot be considered at all tangible. Virtually unique among the phenomena addressed in this volume, the designation of intellectual disability is essentially based on a behavioral classification culled from scores on single measures used to operationalize each of two constructs—in this case, primarily the construct of intelligence but often also that of social adaptation. Typically, people who score in approximately the lowest 3% of the population, or two or more standard deviations below the mean, on standardized tests of intelligence and behavioral adaptation are considered to be intellectually disabled. However, the utility of this designation is compromised in two essential ways. One, the cutoff score is entirely arbitrary. Two, the low IQ, or behavioral, scores can be attained for different reasons and with different profiles as evidenced by the study of the handful of the most common of the more than 1,000 possible etiologies, each of which seems to differ considerably from the other conditions and situations associated with intellectual disability (for reviews, see Burack, 1990; Burack, Hodapp, & Zigler, 1988, 1990; Cornish & Wilding, 2010; Dykens, Hodapp, & Finucane, 2001). These group differences are especially apparent in developmental rates and trajectories as well as the profiles of relative strengths and weaknesses across the myriad of cognitive and social skills that are thought to impact intelligence and the many sub- and sub-sub-tests that make up the various different IQ tests and indexes of behavioral adaptation that are used for the diagnosis. Even given the usual within-group differences that are found in any population, the compelling and clearly demarcated group discrepancies on many aspects of functioning highlight the profound and complex developmental effects of the genes–brain–behavior relations associated with each syndrome that virtually swamp any generalized developmental effects of simply lower levels of intelligence and social adaptation (for relevant collections, see Burack et al.,

1998; Burack, Iarocci, et al., 2012; Howlin, Charman, & Ghaziuddin, 2011; Tager-Flusberg, 1999).

With these pervasive group differences across virtually all aspects of being and functioning, the notion of a population of persons with intellectual disability is a mirage. Thus, the phenomenon precludes a science or study of intellectual disability per se but rather would appear to necessitate the invocation of multiple sciences of identifiable populations that differ meaningfully from each other with regard to etiology, defining features, and developmental trajectories. In this framework, both the concept and the field of intellectual disability are inherently deconstructed from the monolithic framework of a single problem and population to more precise, albeit with the consequent of increasingly complex, conceptualizations and research (Burack, Russo, et al., 2012). This demise of a single science or framework of intellectual disability would seem to come at considerable cost. Prior so-called knowledge about persons with intellectual disability as a whole needs to be forsaken, while the alternative of the imposition of multiple fine-grained fields of study based on clearly differentiated populations inevitably entails considerably more work and would seem to signal the abandonment of any sense, or even hope, of a comprehensive and cohesive field of study. Yet, when the additional work is associated with the imposition of a developmental approach that is premised on the notion of a systemic, organized, and universal system, it provides both more precise information and a unifying framework with which the various fragments of information can be grouped into a meaningful area of scholarship (Burack, 1997; Burack, Iarocci, et al., 2012; Cicchetti & Ganiban, 1990; Cicchetti & Pogge-Hesse, 1982; Karmiloff-Smith, 2009; Zigler, 1969, 1973; Zigler & Balla, 1982; Zigler & Hodapp, 1986).

Diagnostic Criteria and Assessment

In one sense, intellectual disability is relatively easily conceptualized. Across the decades and even centuries of work with persons with intellectual disability, the basic notion has been that a certain percentage of persons function at such low levels of intelligence and social adaptation that they cannot survive or function independently in society, or at least need some intensive external support to do so (e.g., Luckasson et al., 2002; AAIDD, 2010; for reviews, see Rosen, Clark, & Kivitz, 1976; Zigler & Hodapp, 1986). However, intellectual disability is also an odd and elusive behavioral classification as it involves the grouping of an extremely heterogeneous population according to amorphous concepts, arbitrary criteria, and prevailing societal values, all of which have changed often during the past century (for recent discussions, see Bertelli et al., 2014; Salvador-Carulla et al., 2011; Schalock et al., 2010; Shulman, Flores, Iarocci, & Burack, 2011).

Diagnosis and Classification From a Developmental Perspective

Even as researchers and practitioners of intellectual disability discuss relevant issues, including the meaning of intelligence, the role of indexes of social competence in the classification, the measures that should be used for testing, and specific criteria for a diagnosis, the pragmatic reality is that the classification of intellectual disability has historically been entirely determined by IQ, a quantitative measure of the development of the elusive construct of intelligence. Despite the many concerns about IQ scores, they continue to be essential in the demarcation of persons with intellectual disability and in other strategies to identify persons at developmental risk because IQ scores in childhood are seen as reliable indexes of both a child's current rate of intellectual development and of future levels of functioning in relation to one's same-aged peers (Shulman et al., 2011).

The relative reliability among IQ scores at different points in the lifespan captures the developmental essence of intelligence testing and scores. Although IQ scores are typically discussed as measures of individuals' intellectual abilities in relation to those of other persons of the same age, they are historically and essentially indicators of the rate of development of intellectual abilities that is considered both to be consistent at least through adolescence and to be associated with relative level of functioning in adulthood. The developmental nature of IQ is evident in its formula, which involves dividing mental age (MA), the level of cognitive development attained by the individual, by *chronological age* (CA) and then multiplying that number by a constant (usually 100) (for discussions, see Hodapp, Burack, & Zigler, 1990; Zigler & Hodapp, 1986; Shulman et al., 2011). This is fundamentally a measurement of rate as, in this context, CA (the denominator) represents the amount of time taken to attain the level of abilities indicated by MA (the numerator). As a quick analogy, one might think of a common measurement of rate in our everyday lives, that of speed for which we commonly use the equation of kilometers (or miles) per hour. In this equation, the numerator is the specific distance travelled as indicated by the number of kilometers and the denominator is the length of time, as indicated by the number of hours, which has passed during the travels. Both the numerator and denominator grow in relation to each

other, although the ratio between them varies considerably as it serves both as an indicator of the speed of travel and as a point of comparison. And by definition of rate, faster speeds are associated with ratios in favor of the numerator over the denominator. For IQ, the numerator MA is the developmental distance traveled by the individual in their attainment of cognitive abilities and the denominator CA is the length of time that the individual has lived. In this case, a greater numerator, or more distance travelled, in relation to a smaller denominator, less time passed, indicates faster developmental growth. Clearly a child who attains the types of skills common to a 6-year-old in 6 years, and therefore has an IQ of 100 according to our developmental formula, is developing faster than a child for whom it takes 8 years and has an IQ of 75 but slower than one for whom it took only 5 years and who has an IQ of 120.

In terms of long-term consequences, these rates of development are highly correlated with IQ scores and related levels of functioning throughout the rest of the lifespan. Thus, slower development and, therefore, lower IQ scores in childhood are inevitably associated with lower scores on IQ tests and generally lower levels of functioning in adulthood. IQ scores are typically standardized in that they are normed across a representational sample, and, thereby reflect a statistically calculated average for a specific level of functioning at a given age or period in life. Within this context, the primary criterion for the designation of intellectual disability generally involves a cutoff score on a standardized IQ test that is associated with some statistical designation. This cutoff score is usually 70, which is two standard deviations below the mean for the general population for which a mean of 100 is statistically designated. According to this statistical designation, persons with intellectual disability should represent approximately the bottom 3% of the population in terms of IQ scores, although the number of persons who are actually diagnosed often varies in relation to income level of country (Carulla et al., 2011), age of the individual (Hodapp & Zigler, 1986), and the use of social adaptation criteria in addition to the IQ score for the diagnosis (MacMillan, Gresham, & Siperstein, 1993; Switzky & Greenspan, 2006).

The Arbitrary and Amorphous Nature of the Criteria for the Diagnosis of Intellectual Disability

This variability in the specific number of persons who meet this criterion might raise some concerns about the application of two standard deviations below the mean IQ as the cutoff point for the diagnosis, except for the fact that this designation is entirely arbitrary and has no inherent scientific significance with regard to differentiating functioning level among individuals. Rather, the most meaningful aspect of the score is its statistical convenience as the commonly used nomenclature of standard deviations allows for an easily described percentage of persons. As the standard deviations on common IQ tests represent 15 points, persons with IQs just above (i.e., 71, 72, 73) and below (69, 68, 67) the designated cutoff scores do not differ significantly, either statistically or pragmatically, from each other, whereas the differences among individuals within the range of either intellectual disability, with possible IQs of 0–70, or of so-called typical functioning, with possible IQs of 71 and above, are often vast and can encompass several standard deviations. If that is the case, why are IQ cutoffs imposed? The primary rationale is that some criterion is needed as a standard for social policy and decisions about who should receive specialized services. In this way, the designated score which is based on a statistical model of the real world distribution of IQ scores, and thereby level of functioning, offers a rough estimate of the number of persons who should be and are eligible for some combination of additional funding, resources, services, and supports from governmental and other service agencies. The delineation of intellectual disability then is not a scientific one, but rather one that is largely dependent on societal values and discourse, as well as the resources that are made available to support persons with intellectual disability.

The extent to which the designation of intellectual disability is an amorphous and arbitrary concept is evident in that the specific cutoff and the associated definition has been modified at least nine times over the past 100 years in the United States (AAMR, 2002; Harris, 2005; Zigler & Hodapp, 1986) and is once again revised in the newest versions of both the American-based, Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5) (APA, 2013), and the International Classification of Diseases (*ICD*) (Bertelli et al., 2014; International Advisory Group for the Revision of *ICD-10* Mental and Behavioural Disorders, 2011; Salvador-Carulla et al., 2011). These changes in both the diagnostic criteria and the nomenclature are due to many different "real" factors including new knowledge regarding the causes and types of intellectual disability, the perceived significance of social competence and adaptive behaviors, perspectives on eventual outcomes and well-being of persons with intellectual disability, attitudes of societies and policy makers toward individuals' dignity and roles in the community, and pragmatically the resources available for services and intervention. Yet, they also highlight the arbitrariness of

the designation and the influence of factors external to the individuals with the diagnosis.

The most blatant example of the arbitrariness of the criteria was evidenced at the beginning of the 1960s. With the emerging zeitgeist of the time on the promotion of social justice and the desire to improve the lots and lives of those who were deemed less fortunate, the IQ cutoff score was changed from 70, two standard deviations below the mean of 100, to 85, one standard deviation below the mean, by the American Association on Mental Retardation (Heber, 1961). Accordingly, the percentage of persons diagnosed with intellectual disability grew from approximately 2–3% of the population to 16%. In the United States alone, with a population of approximately 200 million at the time, that meant a jump of about 26 million people, from around 6 million to approximately 32 million, who fell within the parameters of a diagnosis of intellectual disability (Zigler & Hodapp, 1986). The absurdity that so many people could go to sleep one night without a diagnosis and wake up the following morning meeting the primary criterion of a person with intellectual disability highlights the obvious arbitrariness in the designation and construct of intellectual disability that precludes any notion of some intrinsic condition that can be meaningfully quantified. These points are even further underscored by the subsequent reversion a dozen years later to the original IQ cutoff (Grossman, 1973), thereby shedding the same approximately 26 million people of their diagnosis—as if in a fairy tale in which they go to sleep one night and are magically relieved of their problem, which, of course, they had not suffered from prior to the change in diagnostic criteria a decade earlier (Zigler & Hodapp, 1986). These changes in the diagnostic criteria were certainly well meaning with the initial change occurring in an era of relative affluence and an emergent emphasis on social change with the intention of enabling services for those persons who typically did not meet the criterion of intellectual disability, but were still considered to be at risk as their intellectual functioning was at the low end of the average range. This course of events provides insight into the difficulties of conceptualizing intellectual disability and the extent to which it must be considered in relation to contemporary societal norms and values.

The Latest Incarnation of the Diagnostic Criteria for Intellectual Disability

In the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; APA, 2013), the term *intellectual disability* (also referred to as intellectual developmental disorder [IDD]), intended to reflect deficits in cognitive capacity beginning in the developmental period, replaces the term *mental retardation*, which had long been used in classificatory schemes such as those of the American Association on Mental Retardation (AAMR) and the American Psychiatric Association for the *DSM*. This revised terminology brings the *DSM* into alignment with the World Health Organization's *International Classification of Diseases* (*ICD*) and other professional disciplines (Salvador-Carulla & Bertelli, 2008; Salvador-Carulla et al., 2011). Intellectual disability is also now the term of choice for public policy discourse by influential groups representing people with intellectual disabilities such as the American Association on Intellectual and Developmental Disabilities (AAIDD, formerly the AAMR; Schalock et al., 2011).

In addition to the revisions in the nomenclature, the changes and revisions to the *DSM* with regard to persons with intellectual disability stem from joint efforts of the American Psychological Association and the National Institutes for Mental Health to expand the scientific basis for psychiatric diagnosis and classification (http://www.dsm5.org/about/Pages/DSMVOverview.aspx). The revisions in the *DSM-5* are based on a comprehensive review of scientific advances, targeted research analyses, and clinical expertise. For example, one of the primary changes in the *DSM-5* involves a shift from a categorical to a more dimensional system. In the earlier versions of the DSM, disorders were described by category, with a specific list of symptoms within each domain (e.g., communication). In this categorical system, a person either displayed a symptom or they didn't, and the presence of a certain number of symptoms was required for a diagnosis. The newly published *DSM-5* involves dimensional assessments that allow clinicians to rate both the presence and the severity of the symptoms, such as very severe, severe, moderate, or mild.

As *DSM-5* is no longer based on a multiaxial classification system, intellectual disability is no longer listed as an Axis II disorder but rather is classified as a neurodevelopmental disorder of brain development. Both *DSM-5* and the AAIDD use the consensus definition of intelligence as a general mental ability that involves reasoning, problem solving, planning, thinking abstractly, comprehending complex ideas, judgment, academic learning, and learning from experience. However, the term "intellectual disability" as used by the AAIDD is a functional disorder, explicitly based on the WHO International Classification of Functioning (ICF). Within this framework, the extent of disability is evaluated within particular contexts for which the focus is on the supports needed to normalize

an individual's life to the extent possible (Schalock, Borthwick-Duffy, Bradley et al., 2010).

In previous versions of the *DSM*, the extent or severity of intellectual impairment was denoted by the levels of mild, moderate, severe, and profound. Whereas these levels of severity will likely remain as central to the new *ICD-11* system, specifiers (i.e., mild, moderate, severe and profound) are used in *DSM-5* instead of subtypes to designate the extent of adaptive dysfunction in academic, social, and practical domains. Within the AAIDD disability model, the focus is on assessment of the supports needed to accommodate to the specific setting (e.g., home, community).

The *DSM* criteria of an IQ score below 70 and low adaptive functioning do not change for the diagnosis of intellectual disability, but the diagnosis involves a greater reliance on adaptive functioning with greater consideration about how intelligence is applied to the functions of everyday life (*DSM-5*). The age of onset is no longer specifically defined as before 18 years and is replaced with onset during the developmental period. However, intellectual disability is distinguished from neurocognitive disorder, which involves a deterioration of cognitive functioning (e.g., dementia) with late onset. In addition, an overall adaptive functioning score of two standard deviations below the mean is no longer necessary, as the criteria is met when at least *one* domain of functioning—conceptual, social, or practical—is sufficiently impaired, based on an assessment of adaptive functioning, that ongoing support is needed. Under exceptional circumstances when standardized assessments cannot be used, as in the case of persons with sensory or physical impairments, a diagnosis of unspecified intellectual disability may be applied to individuals with significant adaptive functioning impairments (APA, 2013).

Even as the revisions to the *DSM* were welcomed by some stakeholders, they elicited criticisms from others. For example, the AAIDD raised the concern in an open letter to the president of the American Psychiatric Association (http://aaidd.org/docs/default-source/comments/aaidd-dsm5-comment-letter.pdf) that the new proposed changes to the criteria for intellectual disability would cause confusion, suggesting that the new boundaries are not as clear as in the *DSM-IV*. For example, the change in the criteria in *DSM* from necessitating that the IDD be present before 18 years of age, to the proposed revisions that all symptoms must have an onset during the developmental period, leaves the age at which the developmental period ends open to interpretation. The AAIDD suggests that this will result in the inconsistent use of developmental periods across jurisdictions. It also took issue with the use of the terms adaptive behavior and adaptive functioning as potentially confusing. According to the AAIDD, adaptive behaviors are the conceptual, social, and practical skills a person may have, whereas adaptive functioning is how well, or independently, the person is able to use those skills to handle common demands in life. Thus, in an appeal to John M. Oldham, the president of the *DSM-5*, the AAIDD argued that the *DSM-5*'s substituting of adaptive *functioning* for adaptive *behaviors* as "communication, social participation, functioning at school or at work, or personal independence at home or in community settings" was not consistent with the AAIDD position nor with the current psychometric literature, and was problematic because it did not adequately capture functioning but rather emphasized the individual's skills (http://aaidd.org/docs/default-source/comments/aaidd-dsm5-comment-letter.pdf). Similarly, the changes in the mutiaxial diagnosis also posed a concern for clinicians. For example, Harris (2013) highlighted the high prevalence of psychiatric disorders in people with a diagnosis of intellectual disability and suggested that both diagnoses are often warranted. However, the elimination of the multiaxial classification and removal of Axis II in *DSM-5* may result in clinicians overlooking diagnoses of mental health disorders, such as anxiety disorder or depression, among persons with intellectual disability.

The Application of the Diagnostic Criteria

The continual fine-tuning of the diagnostic criteria and system represents evolving synergy of professional and societal influences on the ever-changing ways that persons with intellectual disability are viewed, understood, and supported by those around them. As certain problems are addressed, other limitations in the process continue to be identified (Charman, Hood, & Howlin, 2008). For example, even into the twenty-first century, disproportionate numbers of minority children were still being diagnosed with mild intellectual disability as intelligence tests often underestimate the abilities of these children, who also typically fail to meet the dominant culture's expectations concerning academic performance (Hays, 2001; Valencia and Suzuki, 2001). In addition, other non-cognitive factors, such as child's health history, physical impairments, motivation levels, and social milieu must be considered when assessing intellectual abilities as they may inhibit performance on IQ tests or other cognitive tasks, especially among children from atypical or non-majority backgrounds. These types of concerns regarding the narrow focus of, and potential external influences on, intelligence

tests and their use as an exclusive vehicle for defining intellectual disability was the motivating reason for the initial insistence of the American Association of Mental Deficiency (AAMD) (later the AAMR and AAIDD) that low scores on adaptive behavior be included, along with low IQ scores, in its definition of intellectual disability (Borthwick-Duffy, 2007). Accordingly, traditional methods of examining cognitive and adaptive abilities are now supplemented with a thorough examination of the child's developmental history, family history, and social and cultural environment. A broader picture of the child's developmental status is obtained with parent and teacher interviews and evaluations of medical and school records. For example, information about the child's physical problems, peer interactions, social skills and emotional state can be productively used in conjunction with more formal assessment methods, despite their somewhat limited reliability and validity. Consequently, within the framework of a multifactorial model of assessment, the evaluation of intellectual disability is increasingly taking place within an interdisciplinary social developmental framework.

The emphasis is on providing a diagnosis as early as possible to identify the child's specific needs, to ascertain the required services, and to facilitate communication across the team of relevant professionals and among family members. However, this process is not without its problems especially as it can also stigmatize the child if it leads to unwarranted negative projections by professionals and parents about the child's potential. Thus, professionals need to be sensitive to the effects and limitations of the label and recognize that intellectual disability only captures specific aspects of the individual. As the manifestation and outcomes of the key symptoms of intellectual disability vary across the lifespan (Zigler & Hodapp, 1986), a comprehensive assessment program should be used to follow the individual through many of the key periods of development. Current social and behavioral models are characterized by an emphasis on the need for repeated assessments to evaluate the child's changing developmental status and needs, the impact of medical treatments, the appropriateness of educational placements, and the effectiveness of educational programming. This type of approach to assessment captures the dynamic and changing quality of development as well as its social nature. In addition to their discrepancies in cognitive functioning, persons with intellectual disability also differ with regard to their physical, social, and emotional characteristics as well as in their relations with their families and the broader environment.

THE ORIGINS OF THE DEVELOPMENTAL APPROACH TO THE STUDY OF INTELLECTUAL DISABILITY

As with virtually any aspect of scholarship, the developmental approach to intellectual disability has neither a clearly identifiable start date nor even a universally accepted origin. Thus, in a somewhat, but certainly not entirely, arbitrary fashion, we choose an auspicious event that both provided a conceptual link to the essential scholarly antecedents to the field and generated a foundational and vital body of research that transformed the research on persons with intellectual disability by grounding it in developmental theory and methodology. The event was Edward Zigler's 1967 publication of a conceptual piece, "Familial Mental Retardation: A Continuing Dilemma," which appeared in the prestigious general scientific journal, *Science*, at a time when the study of intellectual disability (or mental retardation as it was called at the time) was rapidly growing as a distinct, but largely circumscribed, field. Zigler used that article and a soon-to-follow sister article (Zigler, 1969), "Developmental Versus Difference Theories of Mental Retardation and the Problem of Motivation," which was published in the *American Journal of Mental Deficiency* as forums to challenge the prevailing (so-called) *defect approach* that characterized virtually all of the other research on intellectual disability at the time and continued to influence the field significantly into the 1980s and to some extent even until today (for a collection of pieces on the defect theories and early statements of the developmental approach, see Zigler & Balla, 1982).

The defect approach was largely characterized by a monolithic framework in which intellectual disability was seen as a single entity that was essentially caused by one or more of any number of proposed defects that were common to all persons with the diagnosis. Typically in this approach, cognitive and neuro-cognitive functions or abilities were the primary focus as the empirical work in the field was largely characterized by a race to identify the deficit that was the primary cause or marker of reduced intellectual functioning. Those who undertook this frantic search emphasized broad constructs of cognition that were considered to be essential across all domains of functioning, including cognitive rigidity, memory processes, discrimination learning, and attention–retention capabilities, among many others (for reviews of these approaches and their inherent problems from a developmental perspective, see Burack, 1990; Zigler, 1967, 1969; Zigler & Balla, 1982). With the use of experimental paradigms that were sophisticated for the time, researchers presented evidence

of deficient performance in virtually all of these areas of functioning, and each specific defect was touted as the central cause of intellectual disability. Unfortunately, the evidence was consistently *fatally* flawed as the researchers failed to consider essential and seemingly obvious conceptual and methodological issues, such as the inherent differences in developmental level of functioning between persons with and without intellectual disability of the same CA, the multiplicity of etiologies associated with intellectual disability, the uniqueness of each etiology with regard to phenotypic expression, and social factors related to the life experiences of persons with intellectual disability that could affect performance on experimental tasks (for reviews, see Burack et al., 2001; Burack, Dawkins, et al., 2012; Zigler, 1970, 1973; Zigler & Balla, 1982).

In critiquing and debunking the various claims of the defect theorists, Zigler and colleagues (e.g., Hodapp, Burack, & Zigler, 1990; Zigler & Balla, 1982; Zigler & Hodapp, 1986; Zigler, 1967, 1969) highlighted the conceptual and methodological concerns as the hallmarks of a nascent approach to intellectual disability that would be based on classic developmental theory. The fundamental principles of what would become known as the developmental approach to intellectual disability were based primarily in the previous few decades of developmental theorizing by Heinz Werner and Jean Piaget, but also in two centuries of relevant history of medical scholarship, more contemporary interpretations of statistical analyses of the plotting of IQ scores, and the social-political zeitgeist of the era. In their original and subsequent iterations over the past half-century, Zigler and others, including especially Dante Cicchetti, John Weisz, and Robert Hodapp, contributed immensely to a science and transformative understanding of intellectual disability that were both more precise with regard to the development and functioning of each individual and more humanistic in that they were framed within notions of development that are universal to all persons.

In his initial seminal papers, Zigler (1967, 1969) proposed four principles that both challenged the dogma of the time regarding persons with intellectual disability in one or more ways and that continue to be essential guidelines for current work almost a half century later, albeit in more nuanced and fine-tuned ways of thinking that have developed in the interim since their original articulation. One, the notion that functioning, development, and developmental trajectories differed according to etiology was consistent with centuries of evidence of meaningful differences in behavior in relation to the source (etiology) of the intellectual disability, but challenged the monolithic framework of intellectual disability as a specific disorder and of the population of persons with intellectual disability as a single population that prevailed in the 1960s–1980s and continues to be at the heart of even some contemporary research. Despite resistance from leaders in the field to any type of etiological differentiation (for a review of examples of the opposition to this innovation by leading scholars in the field, see Burack, 1990), Zigler's (1967, 1969) two-group approach involved the delineation between persons whose intellectual disability is due to familial factors such as genetic transmission of intelligence and those for whom it is due to some type of organic insult. This dichotomy would presage a multiple group, or even a 1,000+ group, approach fueled by evidence of differences in development across virtually all aspects of functioning (i.e., cognitive, language, social, emotional) (e.g., Burack 1990; Burack, Hodapp, & Zigler, 1988, 1990; Burack, Russo, et al., 2012; Dykens, Hodapp, & Finucane, 2000; Howlin, Charman, & Ghaziuddin, 2011; Tager-Flusberg, 1999). The need for this type of precision continues to grow as evolving technology continues to enhance our abilities to identify, highlight, and compare sub and sub-sub groupings of specific etiological groups (e.g., Romano et al., 2014; Dimitropoulos, Ferranti, & Lemler, 2013) as well as sub- and sub-subcomponents of the various domains of everyday functioning (e.g., attention, working memory, language, social skills) (Iarocci, Porporino, Enns, & Burack, 2012; Jarrold & Brock, 2012; Russo, Dawkins, Huizinga, & Burack, 2012; Vicari, 2012).

Two, grounded in the developmental theories of Jean Piaget (1970) and Heinz Werner (1948, 1957), Zigler's (1967, 1969) adherence to the traditional developmental principles of an organized, coherent, and systemic organism led to the delineation of universal patterns of developmental sequences and structures among persons with familial intellectual disability, those whose low IQ scores seem to arise from the genetic transmission of intelligence rather than any type of physiological or organic "insult" (for a discussion, see Zigler & Hodapp, 1986). According to Zigler, development, at least in this group which represents essentially the "purest" form of intellectual disability that is unaffected by specific organic insult, unfolds in a typical way but at a slower rate and with a lower asymptote. This view that the integrity of development is maintained even in the face of extreme delay contrasted markedly from the difference or defect approach in which persons with intellectual disability were discussed virtually always within the framework of differences rather than of similarities or universalities in relation to others. In the two decades following Zigler's initial articulation of the

developmental approach, the notion of intact but delayed development would be tested extensively by Weisz and colleagues (Weisz, 1990; Weiss, Weisz, & Bromfield, 1986; Weisz & Zigler, 1979) and extended conceptually to include persons with Down syndrome by Cicchetti and colleagues (Cicchetti & Beeghly, 1990; Cicchetti & Pogge-Hesse, 1982; Cicchetti & Sroufe, 1976, 1978; Wagner, Ganiban, & Cicchetti, 1990). This latter extension to include persons with Down syndrome within a developmental framework revolutionized the developmental approach to intellectual disability by the de facto inclusion of all persons with some type of organic etiology, whose impairments and profiles of functioning seem qualitatively different from the typical population. In an era of considerable debate and discussion about the integrity and legitimacy of developmental theory (for a discussion, see Bronfenbrenner, Kessel, Kessen, & White, 1986), it also would lead to an essential expansion of developmental theory to a more liberal approach that would include more variability, at least in terms of group differences, than was considered in the more conservative classic developmental approaches articulated by Zigler (Cicchetti & Pogge-Hesse, 1982; Cicchetti & Ganiban, 1990; Hodapp, Burack, & Zigler, 1990). This contribution can also be seen as essential to a more nuanced understanding of the extent to which various aspects of development are related to each other in an inherent versus a happenstance manner (Hodapp & Burack, 1990, 2006) and as the precursor to neuroconstructivism (Karmiloff-Smith, 1998, 2009) and other approaches focused on the trajectory of gene–brain–behavior relationships within specific etiological groups (for examples regarding Williams syndrome, see Elsabbagh & Karmiloff-Smith, 2012; Landau, 2012; for an example regarding *fragile X*, see Cornish, Bertone, Kogan, & Scerif, 2012).

Three, Zigler's emphasis on mental, rather than chronological, age in experimental and observational comparisons between persons with and without intellectual disability led to essential changes in the empirical study of intellectual disability with more fine-tuned questions regarding group differences in specific areas of functioning that could not simply be attributed to more general a priori differences in functioning between the groups. In noting that the finding that persons with intellectual disability perform worse than typically developing individuals of the same CA is circular, Zigler (1967, 1969) highlighted the futility and obvious methodological flaws of the defect approaches that unfortunately persist to some extent even until today. These approaches were derived largely from the inevitable finding of deficits among persons with intellectual disability who were compared with typically developing persons of the same CA—findings that simply confirmed the obvious conclusion that lower functioning persons perform at lower levels than higher functioning people. With the increased influence of developmental considerations, the matching of persons with and without intellectual disability has become increasingly fine-tuned as groups are often now matched on a measure related to the domain of functioning being studied, thereby further diminishing the possibility that findings of differences or similarities are a confound of the a priori relative strengths or weaknesses associated with specific etiological groups (for relevant discussions, see Burack, 1997, Burack et al., 2012; Burack Iarocci, Flanagan, & Bowler, 2004; Jarrold & Brock, 2004; Karmiloff-Smith, 2009).

Four, the inclusion of the social-motivational personality factors served to emphasize that the understanding of persons with intellectual disability needed to involve the whole person. Zigler (1967, 1969) highlighted that the life experiences of failure, exclusion, and segregation that are common to persons with intellectual disability (as well as to other commonly marginalized populations) have profound effects on each individual. Zigler even argued that apparent deficits found among persons with familial intellectual disability as compared with typically developing persons of the same MA could be the consequences of responding styles adopted by persons with intellectual disability because of their experiences (for reviews, see Merighi, Edison, & Zigler, 1990; Zigler & Bennett-Gates, 1999). These outcomes were most apparent among persons with intellectual disability who were institutionalized, a far more common occurrence when Zigler was writing than it is today although the implications of segregation and exclusion are still pressing issues.

These four transformative principles of the developmental approach, as initially articulated by Zigler (1967, 1970, 1973) and as developed over the years by him and others, comprise the guiding framework for our discussion both of persons with intellectual disability and of the science in which they are studied. We use these principles of the developmental approach as a framework for interpreting both essential historical and contemporary issues in the study of intellectual disability, and highlight ways that the approach has itself developed since its original articulation a half century ago to provide an increasingly fine-tuned and sophisticated science. Conversely, consistent with Cicchetti's (1984) premise that typical and atypical development are mutually informative, the challenges faced in the application of developmental principles to intellectual disability provide insight into essential ways that developmental theory can be adapted (Burack, 1997;

Cicchetti & Ganiban, 1990; Cicchetti & Pogge-Hesse, 1982; Hodapp & Burack, 1990).

THE TWO-GROUP APPROACH AND BEYOND

Zigler's (1967, 1969) original delineation of the two-group approach was ironic in that it hearkened back to even more precise medical and social classifications of intellectual disability that predated it by decades and even centuries, while challenging a contemporary field that was considerably less fine-tuned. Although Zigler's dichotomy between familial and organic intellectual disability was an essential enabler of the deconstruction of the field of intellectual disability, it can be seen as somewhat of a retreat from more fine-tuned, albeit not always accurate, diagnostic and classificatory schemes dating back centuries (for reviews, see Burack, 1990; Scheerenberger, 1982). As early as the end of the sixteenth and beginning of the seventeenth century, the Swiss physician Felix Platter identified two broad groupings of persons with intellectual disability. He described one group of individuals as simple-minded since infancy and the second as those persons born with identifiable physical anomalies that were the manifestations of underlying organic disorders that were the source of the intellectual disability. This differentiation between persons with intellectual disability born with and without observable physical and physiological problems continued to be highlighted in even more precise classification systems by later medical workers interested in intellectual disability. For example, in the latter part of the nineteenth century, both John Langdon Down (1887) and William Wetherspoon Ireland (1877) provided detailed early classification systems in which they distinguished between intellectual disability which appeared to be the consequence of some combination of familial, genetic, environmental, societal, and cultural factors and that which was the outcome of more obvious genetic anomalies or other types of organic insult. Down classified persons with intellectual disability into three general etiological groupings, which he referred to as congenital, accidental, and developmental. Ireland delineated ten categories, nine of which were associated with medical conditions that were linked with intellectual disability, whereas the tenth was labeled as idiocy by deprivation.

In the subsequent classification systems of the twentieth and twenty-first centuries, the number of genetic or organic conditions associated with neurological problems and intellectual disability grew rapidly as a result of increasingly sophisticated technologies and scientific advances. Current estimates include more than 1,000 organic conditions associated with intellectual disability (Hodapp & Burack, 2006), although the meaningfulness of that number is diminished by the realization that current technology increasingly allows us to identify the substantial effects on performance of even relatively subtle neurological or physiological differences across even persons with the same syndrome (e.g., for a discussion of within-group differences among persons with *fragile X*, see Romano et al., 2014; for a discussion of genetic subtype differences among persons with Prader-Willi syndrome, see Dimitropoulos, Ferranti, & Lemler, 2013).

Zigler's Emphasis on Familial Intellectual Disability

In delineating the two-group approach, Zigler's primary interest as a developmentalist was with the persons with intellectual disability, especially in the mild to moderate range, whose etiology could be considered cultural-familial (for the rest of the chapter we refer to this grouping as familial)—a classification conceptually similar to Platter's simple-minded from birth, Down's developmental in nature, and Ireland's idiocy by deprivation (for twentieth-century systems of classification by etiology, also see Kephart & Strauss, 1940; Lewis, 1933). Consistent with these earlier frameworks, Zigler argued that some combination of familial-genetic and environmental factors affect the development of intelligence and the occurrence of intellectual disability among this group (Hodapp & Dykens, 2001; Zigler & Hodapp, 1986). As predicted by Zigler and Hodapp, current conceptualizations provide increasingly complex but precise frameworks of the genetic transmission of intelligence and its relation to the environment in general and especially in relation to the occurrence of familial intellectual disability (for discussions, see Iarocci & Petrill, 2012; Shulman et al., 2011).

Persons with familial intellectual disability are characterized by IQ scores that are typically in the mild, or sometimes high moderate, range, as they represent a statistically expected downward extension of the typical IQ range and can be thought of as those who were simply at the low end of the normal distribution of IQ (Lewis, 1933; Pearson & Jaederholm, 1914; Penrose, 1963; Zigler, 1967). According to Zigler's conceptualization, familial intellectual disability is simply the case of development that occurs at a slower rate but along the normal continuum of intellectual development. This is consistent with the observation that both individuals with familial intellectual disability and persons with IQs in the lower end of the typical range are likely to have at least one parent with an IQ in or near the range

of intellectual disability (Broman, Nichols, Shaughnessy, & Kennedy, 1987; Hodapp & Burack, 2006; Zigler & Hodapp, 1986). The lack of clear genetic or physiological markers for the children who fit the criterion for familial intellectual disability was underscored a century ago as scores on the early Binet intelligence tests of school children showed neither a natural split nor any significant differences between the children at the lower end of the normal distribution of IQ and a group of typical school children (Pearson & Jaederholm, 1914). This point was reiterated shortly thereafter by Lewis (1933), who argued (in the terms of his time for the group of persons we refer to as those with familial intellectual disability) that there "seems to be a close biological kinship between the subcultural defective and the main body of normal persons . . . " (p. 300), and later by Tarjan (1960), who noted (in the terms of his day for the group of persons we refer to as those with familial intellectual disability) that the "socioculturally deprived" group of persons with intellectual disability blend "gradually into the continuum of the general population" (p. 60; see also Dingman & Tarjan, 1960).

The Politics of Eugenics in Conceptualizing Intellectual Disability Associated With Familial Transmission

The notion of the familial transmission of intelligence has been a historically essential, albeit stigmatizing, aspect of the work with persons with intellectual disability (see Rosen et al., 1976; Siperstein, Norkins, & Mohler, 2007; Zigler & Hodapp, 1986). This focus was highlighted by the advocates of the eugenics movement who, in the late nineteenth century and beginning of the twentieth century, reported on supposed family lines in which feebleminded-ness, criminality, and other forms of behavior that were considered to be generally immoral were linked across generations of families (for a discussion, see Shulman et al., 2011). In one particularly often cited example, Arthur Estabrooks (1916) used the sociologist Robert Dugdale's (1877; Dugdale, Harris, & Giddings, 1910) report on the criminal history of the so-called "Jukes" family from upstate New York to make the case that the procreation of persons with lower intelligence was detrimental to society. Ironically, Dugdale's report was originally intended to be used as evidence for the need for better social welfare and improved environments for persons from these backgrounds, but was twisted to support the argument for legal restrictions on their opportunities to reproduce.

The claim that allowing persons with intellectual disability to procreate was detrimental to society was particularly forcefully advocated by the twentieth-century eugenicist Henry Goddard (1912), who argued in his influential book *The Kallikak Family: A Study in the Heredity of Feeble-Mindedness* for the key role of heredity in feeblemindedness. In a post hoc recreation of the supposed genetic tree of an American Revolutionary War hero named Martin Kallikak Sr., Goddard compared Kallikak's descendants from an evidently feebleminded woman whom he met on his way home from the war and his descendants from his wife who was assumed to be typically intelligent. Goddard claimed that a particularly high percentage of Kallikak's 480 descendants from the feebleminded woman could be labeled as socially problematic as he identified that 36 were illegitimate, 33 were sexually immoral, 24 were confirmed alcoholics, three were criminal, three were epileptics, eight kept houses of "ill fame," 82 died in infancy. In contrast, he claimed that all but three of the 496 descendants from Kallikak's wife were considered to be intellectually normal, and generally prosperous and morally upstanding. With these supposed differences between these two lines of descendants from Kallikak as his evidence, Goddard concluded that levels of intelligence, sanity, and morality were hereditary, and preached that persons classified as "feebleminded" should be prohibited from procreating to prevent the spread of intellectual disability and its associated deleterious effects on society. The scientific integrity and merits of Goddard's work have certainly been questioned over the years. For example, factors other than inherited feeblemindedness, such as fetal alcohol syndrome, have been suggested as possible sources of the generally deleterious outcome of many of Kallikak's descendants (Karp et al., 1995). Yet, despite the criticisms of the obviously controversial focus and methodological problems of his work from contemporary perspectives, Goddard's message of hereditary transmission and intrinsic moral shortcomings of persons with familial intellectual disability was to influence the western world through much of the first half of the twentieth century.

Both Goddard's and Estabrook's views on eugenics and intellectual disability are cited as important contributing factors to the passing of sterilization laws in 25 states in the United States between 1907 and 1936 and in the Supreme Court decision that ruled in support of the sterilization laws in Virginia (for a discussion, see Zigler & Hodapp, 1986). Zigler and Hodapp note that the sentiment of the Supreme Court and that of much of the nation at the time was summed up by the eminent Supreme Court justice, Oliver Wendell Holmes Jr., who wrote the majority opinion in support of the forced sterilization of a young woman named Carrie Buck, who was forced by the courts in 1927 to undergo compulsory sterilization because she

was thought to be feebleminded. In his opinion, Justice Holmes wrote, "It is better for all of the world, if instead of waiting to execute degenerate offspring for crime, or let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind . . . Three generations of imbeciles are enough" (*Buck vs. Bell,* 1927). This pronouncement highlights the extent to which the notions of both the genetic transmission of intelligence and the link between lowered intelligence and criminal behavior were instilled in the American psyche in the first half of the twentieth century. Tragically, these pernicious American laws and attitudes would be copied in other places in the world and have even been cited by some as sources of inspiration for the sterilization and extermination practices of the Nazis toward Jews, Gypsies, homosexuals, and others (Kühl, 1994).

The Familial Inheritance of Intellectual Disability

Based on the notion that persons with familial intellectual disability represent a downward extension of the natural variation in intellectual ability, a variety of possibilities related to the interplay of the genetic transmission and environmental influences on intelligence in this population have been forwarded (for reviews, see Hodapp & Zigler, 1995; Iarocci & Petrill, 2012; Simonoff, Bolton, & Rutter, 1998; Zigler & Hodapp, 1986). These include attempts to fine-tune the understanding of both the genetic process in the transmission of intelligence and the interplay between intellectual heredity and environmental influences.

Consistent with the notion that persons with familial intellectual disability meld into the typically developing population, polygenic inheritance models are highlighted in the explanations of the transmission of intellectual disability within families (for a variety of relevant reviews from the past half century, see Gottesman, 1963; Iarocci & Petrill, 2012; Plomin, 1999; Zigler & Hodapp, 1986). According to this framework, many human traits are continuously distributed and are determined by a number of genes that work independently and additively to produce the particular trait whenever normal environmental conditions prevail. Within the framework of combined genetic and environmental contributions to phenotypic outcome, the primary goal is to identify the polygenes that additively accumulate genetic risk and, together with environmental risk factors, increase the likelihood of familial intellectual disability (Zigler & Hodapp, 1986).

In discussing intelligence in relation to familial intellectual disability, Iarocci and Petrill (2012) likened the nature of intelligence to an elastic band, for which environmental conditions may broaden or constrain inherent potential, but only within the limits of the elasticity, or integrity, of the structure (i.e., inherited familial genes). This is consistent with decades of evidence supporting the notions of the interplay between genetic and environmental factors in the developmental outcome of familial intellectual disability (Richardson, Koller, & Katz, 1985) as intelligence is classically thought to emerge through the coalescence of inherited developmental structures and the organism's ongoing and active engagement with the environment (Shulman et al., 2011). This relationship between familial transmission and environmental influence in intellectual disability was specifically examined by Broman et al. (1987) in a longitudinal study of pre- and perinatal causes of intellectual disabilities as they sought to differentiate the developmental trajectories of persons with familial intellectual disability from those with a clear organic etiology. Based on findings of a 12-fold increase in the frequency of intellectual disability among full siblings of children with mild intellectual disability, and significantly more affected relatives than among the siblings of children with severe intellectual disability, Broman et al. concluded that mild, but not severe, intellectual disability shows a familial link with normal variation in general intelligence. When the children were classified according to socioeconomic status (SES), SES level was associated with intellectual disability at 7 years. In the group of children in the bottom 25% of SES, 3.3% scored in the IQ range of intellectual disability, whereas only 1.3% of the children from middle 50% and 0.3% of the children from the highest 25% SES groups scored in that range. This is consistent with other evidence that mild, nonorganic, intellectual disability is found primarily at lower SES levels, whereas the prevalence of moderate to severe intellectual disability (IQ < 50) is generally distributed relatively evenly across SES levels (Tarjan, 1970; Richardson & Koller, 1996).

The clear link between the familial transmission of mild intellectual disability and low SES highlights the complexity of disentangling the relative contributions of the genetic transmission of intelligence and the environmental factors. This transmission of intelligence is not simply the case of the familial passing of genes, but involves a complex relation between the occurrence of low IQ in the family and the environment in which the family lives. For example, children of parents with intellectual disability are more likely to be raised in settings with fewer resources than typically found in contexts that are more conducive to optimal development (Simonoff et al., 1998). This may be particularly exacerbated among minority populations who already may have fewer opportunities to optimize child development because of linguistic, cultural, or other mismatches with the majority culture in educational and other settings. These qualifications

highlight the complexity of understanding either the unique contributions or the confluence of issues related to the genetic heredity of intelligence and environmental effects associated with familial intellectual disability.

Differentiating Among Organic Etiologies: Extending Beyond the Two-Group Approach in the Quest for Increased Precision

Although aware of the several different etiological groups that had been cited in the two to three centuries previously and that advancing technology would help delineate many more, Zigler simply proposed a two-group approach. This approach allowed him to highlight the group of persons with familial intellectual disability for whom he hypothesized that development unfolded in the same way as for typically developing persons, albeit at a slower rate, against the backdrop of persons with organic intellectual disability for whom Zigler argued that specific organic insult precluded any necessity of typical developmental patterns. Whereas familial intellectual disability represented a quantitative difference from so-called typical development because it simply represented the lower end of normal variation in IQ, the organic etiologies associated with intellectual disability reflected a qualitative break due to the physiological anomalies associated with each of them. Although Zigler would eventually collaborate with colleagues both on calls for more precise differentiation among persons with organic etiologies (e.g., Burack, Hodapp, & Zigler, 1988; 1990) and on attempts to apply developmental theory to specific etiological groups (e.g., Hodapp, Burack, & Zigler, 1990; Hodapp & Zigler, 1990), his primary emphasis continued to be on the developmental approach as applicable to persons with familial intellectual disability.

Burack et al.'s (1988; 1990; Burack, 1990) subsequent call for the precise differentiation among organic etiologies hardly seems revelatory from the perspective of today or even from the perspective of the time in which it was written as unique developmental trajectories and characteristics had already been identified, but it was in clear contradiction to the prevailing thinking of the time among the leading researchers of intellectual disability. Even as the defect theorists faded from the forefront of the study of intellectual disability by the 1980s, the prevailing leaders still refused to acknowledge the advantages of studying individual etiological groups (for some quotes by leaders in the field expressing the futility of differentiating by etiology, see Burack, 1990). Goodman (1990) expressed much of the spirit of the time in her argument against Burack et al. (1988) that "it is unhelpful and possibly detrimental to make etiology the cornerstone of a diagnostic system . . . " (p. 466), and that research and intervention would be better served by a focus on other factors, especially level of intellectual functioning. In the interim of the past quarter century, Burack et al.'s position has clearly been vindicated with the ever increasing precision in delineating both etiologies and unique profiles of functioning that are associated with at least those etiologies that are sufficiently common to be studied.

The contribution of differentiating among organic etiologies to the study of persons with intellectual disability is that of precision. And that quest for precision is characterized by the very undevelopmental process of deconstruction of the population of persons with intellectual disability. This process was central to the de facto breakdown of the field of intellectual disability per se, and the advent of essentially a conglomeration of many sciences (Burack, Russo et al., 2012). It involves the bottom-up process of grouping by etiology, in addition to other relevant factors such as age and gender, to better understand the functioning of each individual or group of individuals. Big stories, such as those once promulgated by the defect theorists concerning all persons with intellectual disability, are long abandoned in favor of more precise minutia—the research is focused on increasingly fine-tuned studies of components (and sub- and sub-sub-components) of functioning in specific etiological groups (and sub-groups). These sciences can be framed in at least one of two apparently orthogonal, but also overlapping strategies, with the emphasis on a specific aspect of functioning and the manifestation of its various components across various etiologies (e.g., for reviews on attention, short-term and working memory, executive functions and memory as manifested in different etiological groups, see respectively Iarocci et al., 2012; Jarrold & Brock, 2012; Russo et al., 2012; Vicari, 2012), or with regard to a specific etiological group in relation to their functioning within or across the many different domains, sub-domains, and sub-sub-domains of one or more specific areas (e.g., for extensive reviews of the abilities and impairments of persons with fragile X, Down syndrome, and Williams syndrome in the domain of language, see, respectively, Abbeduto, McGuffie, Brady, & Kover, 2012; Chapman & Kay-Raining Bird, 2012; Mervis, 2012).

The ultimate goals of this approach is to better understand the links among genes (loosely defined), brain functioning, and behavior in the pursuit of providing more information about the specified group, the contributors to specific aspects of functioning, and potential interventions at many different levels. The more precise the better, with improving technology in every aspect of the gene–brain–behavior relationship allowing us to

further deconstruct our understanding of each into even smaller more detailed units or sub-units. As these foci are syndrome-specific (or now even sub-syndrome-specific), the notion of a scientific field of intellectual disability is rendered essentially meaningless. Any attempts to discuss intellectual disability in terms of groups in which persons with different etiologies are included (often referred to as mixed-etiology) are futile as the syndrome-specific patterns offset each other in this hodge-podge, thereby obscuring any meaningful patterns—much like the flavors of the individual ingredients in stew are unrecognizable after they've been cooked together. And, as the flavor of a stew can be altered in relation to the ingredients, so too can the findings vary in relation to the makeup of the etiological mix. Thus, the notion that a so-called mixed etiology group reflects the general population of intellectual disability is fallacious, and the use of these groups as target groups or even as comparison groups must be seen as both study-specific and misleading. Rather, the more instructive approach to furthering our understanding of the significance of the gene–brain–behavior relations in these groups is to extend Cicchetti's (1984) dictum of the reciprocally informative relationship between typical development and atypical development to focus on the reciprocally informative relationship among various types of atypicality, in this case the specific syndromes.

One example of the ways that information from different syndromes can converge to inform both about each other and functioning more generally is exemplified in the study of multiple object tracking (MOT) among persons with Williams syndrome and Down syndrome. According to Pylyshyn (2001), the operations necessary to index and track multiple items at once in multiple object tracking are also necessary for deriving spatial relations. Concordantly, O'Hearn and colleagues (O'Hearn, Hoffman, & Landau, 2010; O'Hearn, Landau, & Hoffman, 2005) found poor tracking performance among persons with Williams syndrome that was consistent with their commonly reported problems on visuospatial tasks. Subsequently, Brodeur, Trick, Flores, Marr, and Burack (2013) hypothesized that if poor MOT performance is always associated with visuospatial deficits, then MOT should be relatively spared among individuals with Down syndrome who display strengths in visuospatial processing relative to other aspects of their cognitive functioning. However, contrary to their predictions, they found that the performance on a MOT task was worse among individuals with Down syndrome as compared with MA-matched typically developing children. In explaining these unexpected findings, Brodeur et al. suggested that tracking deficits may occur for different reasons in the two groups. For example, compared with individuals with Williams syndrome, persons with Down syndrome may display relatively intact object-based selection, but may nonetheless exhibit reduced tracking performance because the temporal resolution of the selection processes is poor, which would create particular difficulties when processing dynamic displays. Another possibility is that object-based selection may be preserved in persons with Down syndrome, but that limitations in executive function may reduce the ability to store information for later report while updating item positions. These post hoc explanations point to the need to specifically fine-tune our understanding both of the strengths in visuospatial functioning among persons with Down syndrome and of the extent to which MOT is generally associated with visuospatial performance. At a more conceptual level, they also highlight the necessity for greater nuance in understanding the abilities and factors that contribute to performance on tasks within a single etiological group and, more complexly, in comparisons across groups.

In retrospect from an era in which research is increasingly informed and fine-tuned by technology such that more and more groupings and subgroupings are defined and studied, Zigler's (1967, 1969) articulation of the two-group approach can be seen as a catalyst in transforming, or deconstructing, the field of intellectual disability into a more precise, albeit increasingly differentiated, science. As evident in the cutting-edge work by Romano et al. (2014) in delineating two biologically and clinically distinct phenotypic outcomes of fragile X using topological data analysis of variations in brain structure and by Dimitropoulos et al. (2013) in identifying differences in language functioning between the genetic subtypes of Prader-Willi, the level of precision and differentiation in the field will continue to increase dramatically. However, as discussed in the next section, Zigler and, to an even greater extent, Cicchetti provide a framework for the integration of these seemingly impossibly fractionated pieces—the fulfillment of Werner's orthogentic principle.

APPLYING DEVELOPMENTAL PRINCIPLES TO THE STUDY OF PERSONS WITH INTELLECTUAL DISABILITY: CLASSIC AND EXPANDED VERSIONS

Zigler and the Classic Developmental Approach

The defining developmental innovation in Zigler's approach to the study of intellectual disability was his imposition of essential classic developmental principles

to the study of persons with intellectual disability, who had previously virtually always been considered defective, impaired, or at least different in some specific way. In citing the organismic-developmental theories of Heinz Werner and Jean Piaget, Zigler (1967, 1969) invoked the notion of universality of the human organism, thereby including the previously excluded group of persons with intellectual disability, at least those with the familial form. Conversely, this approach was also essential to extending classic developmental theory to persons with intellectual disability and, thereby, to provide much needed tests of the theory from the context of atypical development. Even as classic developmental theory, in general, and Piagetian notions, in particular, were under siege throughout the 1960s and beyond as post- and neo- Piagetian scholars, among others, decried the lack of consideration of group and individual differences and even suggested the end of the age of development (Kessen, 1984), Zigler's framework provided compelling, if not sufficient, tests of the universality of classic developmental theory.

Zigler framed his notion of the applicability of the universality of development largely within the context of Werner's (1957) organizational principle of development that "wherever there is life there is growth and development, that is, formation in systematic, orderly sequence" (Werner, 1957, p. 125) and the Piagetian notion of universal sequences of development. These notions resonated especially with Zigler with regard to the population of persons with familial intellectual disability whose lower IQs represent simply a statistically expected downward extension of the typical IQ range as is consistent with the case of any hereditarily transmitted trait (e.g., height, weight). In contrast to the qualitative break that he suggested might be the case with persons with an organic etiology, Zigler hypothesized that the patterns of development of persons with familial intellectual disability should be indistinguishable from those of typically developing persons but that they would unfold at a slower rate and ultimately plateau below the general population mean. Zigler's approach led to two hypotheses of basic developmental similarities, similar-sequence and similar-structure, between persons with intellectual disability and typically developing persons that would be tested extensively by John Weisz and colleagues (e.g., Weiss, Weisz, & Bromfield, 1986; Weisz, 1990; Weisz & Yeates, 1981; Weisz, Yeates, & Zigler, 1982; Weisz & Zigler, 1979).

The Similar-Sequence Hypothesis

The similar-sequence hypothesis reflects the basic tenet of developmental theory that the development of a specific area of cognitive functioning necessarily follows a clear and universally prescribed order of attainment of the relevant abilities (Hodapp, 1990). The sequences can be thought of as the vertical aspects of development since they involve the trajectory of development in relation to the attainment of one or more specific functions, or abilities, over time. In an extensive review of relevant studies, Weisz and Zigler (1979) found that the integrity of typical Piagetian sequences seems well entrenched among all groups of persons with intellectual disability as it is among virtually all other groups of persons (for discussions, see Weisz, 1990; Hodapp & Burack, 2006).

In considering the inevitability of the universality of Piagetian and other developmental sequences, Hodapp (1990) proposed four possible reasons for their universality. One was that psychological, like biological, development involves a process that is consistent with Werner's (1957) orthogenetic principle, in which "wherever development occurs it proceeds from a state of relative globality and lack of differentiation to a state of increasing differentiation, articulation, and hierarchic integration" (p. 126). The case of human fetal development is a classic case in the realm of biological growth as we all begin as a speck of a single cell that lacks any identifiable form, but unfolds with increasingly identifiable internal and external parts that continue to evolve into a complex human being in which all the parts are distinct and at the same time integrated in that they function in an organized coherent way. In an example of the orthogenetic principle in psychological development, children first use only sentences made of single words to communicate, but further along in development use more complex sentences composed of multiple different words combined in infinite combinations, giving rise to more complex communication. As psychological development is constrained and dependent on biological development that is universal, Hodapp suggests that it too must be universal. Hodapp's second argument is based in the logic that since behaviors are sequentially embedded in each other, a child is only able to perform a difficult or complex task by first attaining the necessary skills through the performance of more basic (earlier) tasks. Hodapp's third argument is based on universally shared information-processing capacities that are used to understand and experience the laws and relationships in nature that transcend culture, geography, or language. Hodapp's fourth argument is that the essential task of all cultures is to foster the development of its children and that this quest may involve universal aspects of the environment, regardless of culture or context.

The Similar-Structure Hypothesis

In contrast to the verticality of his similar-sequences hypothesis, Zigler's (1967, 1969) similar-structure hypothesis is relevant to the horizontal dimension of development as it concerns the relations across domains, or areas, of functioning at one or more given points in time. It is based on the classic developmental principle of an organized system, such as espoused by Piaget in his notions of cognitive structure and stage theory, in which aspects of development are meaningfully interrelated and therefore, despite individual variation, consistently emerge and unfold in some universally systematic and hierarchic way with consistent temporal patterns (also see Werner, 1957). In this manner, developmental profiles across domains should, with only minor differences, be consistent across the population of typically developing individuals for any given point in time (age) of development. Thus, also unlike the similar-sequence hypothesis, the similar-structure hypothesis was considered by Zigler to be specific to persons with familial intellectual disability for whom he considered the patterns of development to be the same as in typical development, but to just unfold at a slower rate and to ultimately reach a lower plateau—delayed rather than different (Zigler & Hodapp, 1986). In direct contradiction to the prevailing difference or defect theories of intellectual disability of the 1960s and 1970s, the similar-structure provided the framework for Zigler's expectation that persons with familial intellectual disability, as a group, would show the same level of performance on virtually every aspect of cognitive functioning when compared with typically developing persons at a similar general level of functioning (i.e., MA) (Mundy & Kasari, 1990; Weiss et al., 1986; Weisz, 1990; Weisz & Yeates, 1981; Zigler & Hodapp, 1986).

In a systematic and comprehensive review of empirical comparisons between the performance of persons with intellectual disability and that of typically developing children on Piagetian-type tasks, Weisz and Yeates (1981) found that the similar-structure hypothesis was supported in 90% of the 39 comparisons in the literature in which the appropriate developmental methodological strategies of matching the groups by MA and excluding persons with any indication of organic impairments or genetic anomalies were utilized. Thus, consistent with Zigler's hypothesis that familial intellectual disability is simply a slowed version of typical development, the findings across these studies indicated similar levels of performance by this group on Piagetian tasks in relation to typically developmentally children of the same level of functioning (i.e., MA rather than CA). However, the veracity of the similar-structure hypothesis was questioned by Weiss et al. (1986) in a subsequent analysis of evidence from studies of information-processing, as persons with familial intellectual disability displayed inferior performance as compared with appropriately MA-matched typically developing persons on some tasks of memory, discrimination learning, and learning set, but not on other aspects of information-processing such as concept usage and incidental learning.

Weiss et al.'s (1986) challenge to the similar-structure hypothesis highlights the need to consider the implications of findings of deficits in cognitive functioning among persons with familial intellectual disability as compared with typically developing persons, an occurrence that appears to be more likely with the more precise methodologies associated with study of information-processing (Mundy & Kasari, 1990). Both the areas of functioning and the specific tasks that are associated with the evidence of impairment may be informative about the specific source of the problems on the specific test and about broader issues regarding the general performance of persons with intellectual disability. For example, the number of domains in which differences were found were limited and may be due to extenuating, and potentially confounding, factors in the relevant paradigms as impaired performance only appeared to be found in situations in which the tasks were long and repetitive, lacked ecological validity, and occurred in situations in which certain motivational and personality characteristics can affect performance. This is consistent with Zigler's early conceptualization of the various ways that the effects of a lifetime of experiences of failure affects the performance on experimental and real-life tasks by persons with intellectual disability. In extending this notion of the influence of personality and motivational factors on performance to highlight a "helpless" style of behavior that arises from a lifetime of failure, Weisz (1990) suggested that the discrepancies in performance in the studies cited by Weiss et al. may have been a function of the approach to the task at hand, rather than inherent differences in cognitive processing. Thus, the finding of these group differences seem more of an opportunity to further fine-tune Zigler's point of the necessity of understanding the whole person with intellectual disability than a contradiction of Zigler's similar-structure hypothesis as applied to persons with familial intellectual disability.

Cicchetti's Expansion of the Developmental Approach to Persons With Organic Etiologies: A Focus on Persons With Down Syndrome

Barely a decade after Zigler's (1967) original articulation of the developmental approach to intellectual disability,

Dante Cicchetti and colleagues (Cicchetti & Serafica, 1981; Cicchetti & Sroufe, 1976, 1978) provided its most compelling and far-reaching extension by initiating a program of research with children with Down syndrome that was based in developmental theory and principles. Although their work was focused exclusively on persons with Down syndrome, Cicchetti and colleagues (Cicchetti & Ganiban, 1990; Cicchetti & Pogge-Hesse, 1982) raised the possibility that these principles and theories could be applied to all persons with an organic etiology rather than just to persons with familial intellectual disability as argued by Zigler. As was the case with Zigler's seminal work, Cicchetti and colleagues' innovations were largely based in Heinz Werner's (1957) organismic-developmental approach with its overarching and universal organizational principles that provide meaning to the patterns of development (for a discussion, see Cicchetti & Ganiban, 1990). However, their application of classic developmental theory to persons with Down syndrome and, thereby essentially, to all persons with organically based intellectual disability provided both a much expanded view of development and a more stringent test of the universality of developmental theory than did Zigler's iteration of the developmental approach.

Cicchetti and Pogge-Hesse (1982) designated Zigler's developmental approach to intellectual disability as a conservative one in that it only applied to persons with familial intellectual disability as he excluded those with organically based intellectual disability. The rationale for this exclusion was that "if the etiology of the phenotypic intelligence (as measured by an IQ) of two groups differs, it is far from logical to assert that the course of development is the same, or even that similar contents in the behaviors of two such differing individuals are mediated by exactly the same cognitive processes" (Zigler, 1969, p. 533). In contrast to Zigler's conservative application of developmental theory and principles solely to familial persons with intellectual disability and their apparent typical patterns of development, Cicchetti and colleagues' expanded theory was focused on the search for coherence even across patterns of development that did not conform either to the norm or to the classic developmental theories of Piaget, Werner, and others. This more liberal framework transformed the developmental study of intellectual disability with its de facto inclusiveness of essentially all persons with intellectual disability under the umbrella of universal developmental principles while maintaining the essential ingredient of differentiating among etiologies. The unique patterns of relative strengths and weaknesses across areas of functioning for each specific etiological group could be examined in relation to underlying patterns of development. Rather than delimiting the developmental approach and dismissing the unique development of specific etiological groups as different or impaired, Cicchetti and colleagues (Cicchetti & Ganiban, 1990; Cicchetti & Pogge-Hesse, 1982) sought coherence even as the developmental patterns diverged considerably from the typical (also, see Hodapp, Burack, & Zigler, 1990; Hodapp & Zigler, 1990; Wagner, Ganiban, & Cicchetti, 1990). For example, Cicchetti and Pogge-Hesse argued poignantly that the deficit approach "overlooks the possibility that the behavior and development of retarded children is organized, adaptive, and integrated—just as is the case for nonretarded children and infants. We know that they are retarded; the important and challenging research questions concern the developmental process" (p. 279). They concluded that "organically retarded persons are not only 'different' from nonretarded persons, they are organized in their own right . . . " (p. 313).

The centrality of this framework to the emergence of the developmental approach to the study of intellectual disability was highlighted by the inclusion of theoretically based review chapters by Cicchetti and colleagues (Cicchetti & Ganiban, 1990; Cicchetti & Pogge-Hesse, 1982) in the two initial edited volumes by Zigler and colleagues on the developmental approach (Hodapp, Burack, and Zigler, 1990; Zigler & Balla, 1982) and in a volume edited by Cicchetti and Beeghly (1990) devoted to the development of children with Down syndrome. Concordantly, Hodapp and Zigler's (1990) reframing of the conservative developmental approach to fit with the evidence from persons with Down syndrome (and, by extension, persons with other organic etiologies) in the opening chapter of the Cicchetti and Beeghly volume highlighted that the task of the expanded developmental study of intellectual disability was to seek developmental patterns across all etiological groups.

In broadening the cache of persons with intellectual disability to be studied within the context of the developmental approach, this more liberal developmental approach served to extend the relevance of classic developmental theories by implicitly challenging the common critiques of their deficiencies in accounting for group or individual differences (see Bronfenbrenner et al., 1986; Kessen, 1984). The study of Down syndrome and other etiological groups, with their own specific patterns of development, provides unique opportunities, or experiments of nature, to ask any number of essential questions such as which developmental patterns are necessary and which are happenstance? What skills are related to each

other throughout development and how closely need they be related? Where are alternative developmental pathways possible? Thus, Cicchetti and Pogge-Hesse (1982) argue that the orientation of the discussion about abilities needs to be changed so that "we should study not "does x have y" but rather "in what way does x use y" and does a particular mental structure interact with other mental structures in the same way in one . . . group as in another? (p. 313)"

One approach to this type of more complex, or liberal developmental, framework among persons with intellectual disability was initially suggested by Mundy, Seibert, and Hogan (1984) who borrowed the notion of local homologies, or developmental relationships across tasks that require underlying capacities, from the work on relationships across sensorimotor abilities among typically developing infants by Bates, Benigni, Bretherton, Camaioni, and Volterra (1979). Hodapp and colleagues (Hodapp, Burack, & Zigler, 1990; Hodapp & Zigler, 1990) proposed that this notion of local homologies may be essential to reconciling within an organizational developmental framework the apparent discrepancies, or lack of similar-structure (Weisz & Yeates, 1981), across areas of functioning that are found among persons with Down syndrome and other organic etiologies. Thus, this framework imposes some semblance of conceptual coherence across areas of functioning amid the apparent disconnectedness associated with the myriad of profiles of relative areas of strengths and weakness associated with the different etiologies.

In considering the various contributors to the complexity of the developmental approach to the study of persons with Down syndrome and other organic etiologies, Cicchetti and colleagues (Cicchetti & Ganiban, 1982; Cicchetti & Pogge-Hesse, 1982) highlighted that etiological groups could provide specific insights into the ways that both genes and organic function lead to behavioral outcomes. This notion is foundational to the contemporary notion of genes-brain-behaviors with specific etiological groups, each of which provides the opportunity for understanding the roles of specific genes and genetic structure as well as of organic function on behavior. As predicted by Cicchetti and colleagues, these endeavors would be enhanced by advances in technology and methodology that both allow for more extensive and precise groupings of persons with organic etiology and more sophisticated science with increasingly fine-tuned behavioral, physiological, and neuropsychological paradigms.

One particularly compelling expression of Cicchetti's vision was the "neuroconstructivist" approach that was promoted by Annette Karmiloff-Smith (1998, 2009; Mareschal et al., 2007; Westermann et al., 2007). Building upon the Piagetian notion of constructivism, with the child as an active agent in constructing his or her own cognitive structures through exploration and engagement with the environment, the neuroconstructivist model was developed and applied to children with organic etiologies associated with intellectual disability. Coined by Karmiloff-Smith (1998), neuroconstructivism brought together Piagetian constructivism with the emerging research on experience-driven neural plasticity. Karmiloff-Smith argued that to understand the cognitive profiles of organic etiologies, researchers needed to consider them within the context of the cascade of neural development. Using the example of Williams syndrome, Karmiloff-Smith et al. (1997) argued that rather than framing this syndrome as a modular disorder with spared language and impaired visual-spatial modules, the unique cognitive profile associated with it is the product of a unique developmental trajectory. As a corollary, Cornish and colleagues (Cornish, Cole, Longhi, Karmiloff-Smih, & Scerif, 2013; Cornish, Steele, Monteiro, Karmiloff-Smith, & Scerif, 2012; for a review, see Cornish & Wilding, 2010) highlighted that groups of persons with different organic etiologies might exhibit different attentional profiles and inhibitory control beginning in infancy, which in turn contribute to different developmental pathways. The neuroconstructivist framework then casts each of the organic etiologies as having genetically determined constraints, which manifest as subtle differences in preferences and biases early in development, steering the child down an etiology-specific developmental pathway that is nonetheless constructed by the child (e.g., for discussions regarding fragile X, see Cornish, Bertone, Kogan, & Scerif, 2012; Cornish, Scerif, & Karmiloff-Smith, 2007; for a discussion regarding Williams syndrome, see Elsabbagh & Karmiloff-Smith, 2012).

In promoting the neuroconstructivist approach, Karmiloff-Smith and colleagues challenge the virtually exclusive dependence on cross-sectional methodologies, with their snapshots of performance at a specific moment in the lifespan, in the quest to better understand intact or impaired performance in the study of specific etiologies. This is consistent with the notion that performance is always relative—relative not only to another group but most important also to past and future performance. Ideally, developmental disorders (and development in general) should be examined longitudinally, although as Karmiloff-Smith (2009) acknowledges the measurement of change over time often needs to be simulated using regression-based approaches due to the pragmatic difficulties inherent in longitudinal studies. The extent to which our understanding of development is constrained by cross-sectional methodology is highlighted

by Cornish et al. (2013) who depicted both a trajectory mapping correlational study and a one-year longitudinal follow-up study of attentional control and working memory among children with fragile X. Whereas the data from the cross-sectional trajectory mapping suggested developmental arrest in working memory and a dramatically slower (relative to typical) but positive slope in relation to MA for attentional control, the longitudinal data indicated similar slopes of improvement for both skills in relation to the performance of the typically developing children.

Another example of the contemporary realization of the need for increasingly sophisticated methodology and precise understanding of the development of gene–brain–behavior relationship within a specific etiological group is Barbara Landau's (2012; Landau & Hoffman, 2007) work on the ways that developmental time is essential to the organization and development of spatial representations among persons with Williams syndrome as well as among typically developing persons. Landau argues that one of the ways in which, genetic etiologies contribute to intellectual disability is in the disruption of the rate of development, but emphasizes that the mapping of developmental timetables in these etiologies needs to be considered in relation to typical development. To illustrate this, Landau argues that the spatial capacities that are strong among persons with Williams syndrome are associated with the ventral stream, which emerges relatively early in the typically developing child, whereas the capacities that are weaker are associated with the dorsal stream, which develops later in typical development. For example, children with Williams syndrome (MA 4–6 years) perform at or above MA expectations on tasks used to measure aspects of spatial abilities that involve the ventral stream, which develops early in typical development (e.g., perceptual matching). Conversely, differences in performance emerge on dorsal stream tasks for which development is protracted in typical development. Based on this evidence, Landau hypothesized that the developmental trajectory of the dorsal stream is slower than that of the ventral stream for persons with Williams syndrome and that it is the exaggerated asynchronous development of the two streams that contributes to their unique profile of spatial abilities.

THE IMPORTANCE OF MENTAL AGE

Considering Developmental Level

In Zigler's (1967, 1969) critique of the prevailing defect approach of the time, the most obvious, and thereby the most troubling, of the essential methodological flaws that he cited as inherent to the defect theorists' research and findings was the emphasis on CA as the point of comparison between persons with and without intellectual disability. The defect theories were based largely on evidence from studies in which the performance of a group of persons with intellectual disability was compared with that of a group of typically developing persons who were matched, or deemed similar, to the first group on the basis of CA. Since persons with intellectual disability are, by definition, lower functioning than those without intellectual disability of the same CA, the outcome of such research is obvious. The persons with intellectual disability would always be expected to perform worse on any experimental task that is appropriate for the level of functioning of the participants and that is sufficiently sensitive to differentiate between groups of persons within the relevant range of level of functioning. Yet, despite their inevitability, findings of group differences based in this methodology were considered essential evidence by the defect theorists in their promulgation of the various impairments that were hypothesized as the core deficits of intellectual disability.

In highlighting one example of the extent to which CA matching research was integral to promoting the defect approach, Iarocci, Burack, and colleagues (Burack et al., 2001; Burack, Dawkins, et al., 2012; Iarocci & Burack, 1998; Iarocci et al., 2012) demonstrated that the commonly accepted notion of a core defect in attentional functioning, which was perpetuated from the 1960s even well into the 1990s, was based largely on empirical evidence in which matching was exclusively based on CA. In addressing this claim in a review of the rather limited empirical evidence available in which the group of persons with intellectual disability were homogeneous with regard to familial status and were matched to the comparison group of typically developing children on the appropriate basis of MA, Iarocci and Burack found no evidence for any attention deficit. Rather, they concluded that the defect approach researchers of attention had promoted "fatally" flawed research and had simply and inevitably found that lower functioning persons functioned at lower levels than higher functioning persons.

Iarocci and Burack (1998) acknowledged that the failure to find impairments in attentional functioning among persons with familial intellectual disability certainly does not rule out the possibility of finding deficits either among persons with familial intellectual disability on different components of attention, with different tasks, or at different ages; or among groups of persons with specific organic etiologies, some of which have been linked to preliminary developmental patterns of attention problems (for recent reviews, see Cornish & Wilding, 2010; Iarocci et al., 2012).

Yet, they and their colleagues highlight that the use of essentially problematic methodology of CA-matching led to the perpetuation of a myth of attention deficit in the study of intellectual disability (Burack et al., 2001; Burack, Dawkins, et al., 2012).

Given the obvious problems with CA-matching, what is the possible justification for the decades-long perpetuation for this fatally flawed methodology? One common argument for CA matching is that it allows for the identification of "spared abilities" in specific areas of functioning (for a discussion of the arguments in favor of CA matching and their fatal flaws, see Burack, Russo, et al., 2012). The proponents of CA matching argue that if persons with intellectual disability perform similarly to a CA-matched group of typically developing persons in a specific area of functioning then functioning in that area could be considered to be uniquely spared. Unfortunately, this reasoning is inconsistent with the basics of experimental developmental research. The failure to find differences between groups can rarely, if ever, be considered unqualified, or even strong, evidence that the groups perform similarly. Rather, this type of finding is more likely the consequence of one or more methodological constraints. In the case of research with persons with intellectual disability, the failure to find group differences is often because the participants do not function at the developmental levels at which differences in the specific area of functioning might optimally be found. For example, if an area of functioning emerges at age X, testing participants considerably prior to age X would not elicit group (or individual) differences since the area of functioning would not have yet developed for even the typically developing persons, and therefore both the typically developing children and children with intellectual disability would display apparently low levels of performance. Concordantly, differences would also be unlikely to be elicited with participants who are significantly older than X as the persons with intellectual disability would have had ample opportunity to attain the requisite skills even if their development in the specific area of functioning is slower as compared with the typically developing persons. Even in the case when the participants are all at the ideal age to study the emergent area of functioning, differences might not be found because of the lack of sufficient sensitivity of the task to differentiate level of performance among groups. Thus, without more evidence, the failure to find group differences tells us little about the relative abilities of the groups and the case for the sparing of abilities is more likely a consequent of problematic methodology than of any meaningful characteristic of the specific group (Burack, Russo, et al., 2012).

The most obvious matching strategy for comparing groups with different a priori levels of functioning, such as indicated by IQ, is to find a way to equate the groups on a general criterion that is relevant to the aspect of functioning that is being studied. In the study of cognitive and cognitive-related abilities among persons with intellectual disability as compared with those without intellectual disability, the relevant criterion is level of cognitive functioning, or MA, at the time of testing. In this context, the task of the researcher is to find groups of persons with and without intellectual disability that are similar on these measures, which can be accomplished only with groups that are considerably discrepant with regard to CA. Although the persons with intellectual disability are inevitably chronologically older, the strategy of matching by MA diminishes, or even eliminates, the potential criticism that findings of deficits among the persons with intellectual disability can simply be attributed to the generally lower levels of functioning. Rather, the case might be made that the deficit in the area of interest among the group of persons with intellectual disability is evident even when general functioning is equated. This is, of course, a much stronger argument than when the a priori level of functioning differs between the groups, as in the case of CA matching. Thus, the original call to match by MA (see Zigler, 1967, 1969; Zigler & Balla, 1982; Zigler & Hodapp, 1986), or general developmental level, was a meaningful improvement over the CA-matching strategies of yesteryear since the apparent deficits of persons with intellectual disability could not be simply attributed to a priori levels of development and functioning.

Although matching on the basis of MA represents an advance in the field, the process of matching is inherently flawed (Burack, Russo, et al., 2012; Jarrold & Brock, 2004) as the task of equating such different groups of persons is plagued by the fact that the groups are, in fact, essentially different. In highlighting this point, Burack, Russo et al. note that even in the imaginary scenario in which a person with intellectual disability and a typically developing child would have the exact same MA for a moment in time, they would differ from each other in so many different ways. By definition, the typically developing child would have attained the shared MA at a faster rate and at a younger age, whereas the person with intellectual disability would have lived longer and be more physically and physiologically mature. In addition to the age differences, the two would have had very different life experiences, especially with regard to support and encouragement, successes and failures, and the nature of familial and other relationships. Their futures would also diverge.

In the hypothetical case of an ideal test with perfect sensitivity and reliability in which the two children were perfectly commensurate with regard to level of functioning at a point in time, the typically developing child would surge ahead the moment after.

The inherent limitations in MA matching in the study of persons with intellectual disability are particularly exposed in the study of specific etiological groups, as the unique profiles observed for each of them relegate general scores of MA as insufficient to mitigate against claims of a priori differences between the groups (e.g., Karmiloff-Smih, 2009). In a relevant paper on matching in research with persons with autism, Burack et al. (2004) point out that "no choice of comparison group or matching strategy is perfect, but rather needs to be determined by specific research objectives and theoretical questions" (p. 65). In this context, they and others (e.g., for a detailed discussion, see Mervis & Klein-Tasman, 2004) highlight the need to utilize matching measures that are even more precise than general MA so that the matching is not by some general construct of developmental level but rather is linked to the development of abilities that are pertinent to the specific function or task. This strategy minimizes the chances that differences in performance between the groups might be an artifact of a specific relative strength or weakness in the area of functioning related to the experimental task for one of the groups. As an almost universal manifestation of this approach, researchers typically used measures of performance or nonverbal measures to match groups for studies that involve visuo-spatial processing, whereas verbal measures are most often used as the matching criterion for studies in which verbal abilities are central. However, this more precise strategy is still replete with problems as many experimental tasks involve both visual-spatial and verbal reasoning. Furthermore, the matching measures often lack precision, are often either particularly broad indicators of functioning, or are only tangentially related to the experimental task so that they are only minimally more relevant than general MA to the skills for which they are supposed to control. Despite the seminal methodological advances that arose from Zigler's articulation of MA, rather than CA, as the essential criterion for matching groups in studies with persons with intellectual disability and the subsequent imposition of increasingly precise indicators of matching, Burack, Russo, et al. (2012) suggest that the discussion should be less about "the way" or even "best way" to match, but rather, more humbly, the "least bad way" for the specific context of a given study. This acknowledgment of the inherent limitations with matching strategies is highlighted by the calls by some developmentally-oriented researchers to supplement, or even supplant, research methodologies based on the matching of groups with those involving regression or longitudinal paradigms (Cornish et al., 2013; Jarrold & Brock, 2004; Karmiloff-Smith, 2009).

THE STUDY OF THE "WHOLE PERSON" WITH INTELLECTUAL DISABILITY

The fourth of Zigler's (1967, 1969) primary contributions to the development of the developmental position best highlights the humanistic aspect of Zigler's developmental work (for a discussion, see Burack, 1997). Amid the field's obsessive focus on identifying a central, and inevitably cognitive-based, defect to explain intellectual disability, Zigler further distanced himself from his contemporaries by highlighting the need to focus on the persons with intellectual disability rather than on the phenomenon of intellectual disability and on all the domains of functioning that comprise the whole person rather than on just a specific area (or areas) of deficit. He argued that being a person with intellectual disability inevitably involved life experiences that would affect the way the person behaves and performs in all aspects of their life. However, true to his developmental outlook, Zigler even framed this apparently population-specific consideration within the context of universal developmental issues. The focus wasn't exclusively on the effects of intellectual disability or even on the life experiences of being a person with intellectual disability, but rather was framed within the context of a lifetime of failure, lowered expectations, and, in keeping with the times, institutionalization, all of which were relevant, but not exclusive, issues in the lives of persons with intellectual disability. As with other groups who shared some of these same life history backgrounds, such as persons from historically oppressed and particularly low SES groups, Zigler imagined that certain personality characteristics related to the motivation of the individuals with intellectual disability would develop in relation to the life circumstances and would permeate every aspect of the person's functioning. Although Zigler cited the personality-motivational characteristics as explanations for lower than expected performance for persons with familial intellectual disability on experimental tasks and how they could interfere with optimal task performance, these traits are as, if not more, relevant to virtually every aspect of any person's daily life.

These hypothesized interrelated traits include overdependency, low self-esteem, wariness of others, limited

mastery motivation, reinforcement-seeking, and outer-directedness (rather than innerdirectedness) (for reviews, see Merighi, Edison, & Zigler, 1990; Zigler & Burack, 1989; Zigler & Hodapp, 1986). Each of these styles of behaviors can be seen as a natural outcome for someone one who has lived with constant and consistent failure, little if any positive reinforcement, considerable criticism, lowered expectations, and other inevitable experiences of someone who functions outside the realm of society or fails to meet societal expectations. Yet they are also part of a more universal humanistic approach to understanding behavior as the same traits found among persons with intellectual disability or even others on the fringe are also found among persons in the mainstream society who have experienced failure. From a developmental perspective, the essential point of these characteristics is that they can even be adaptive in the appropriate context. For example, almost all of us utilize an outerdirected strategy in checking what others do when placed in situations that are particularly novel, dining in a restaurant of a different culture for the first time, or complex, dining at a particularly elegant event in which a multitude of dishes, glasses and utensils are provided. In these situations, we typically look around to see what is expected and act in relation to how others do in order not to embarrass ourselves, whereas in other more comfortable or common situations, we tend to behave in a more innerdirected way. In contrast, Zigler noted that persons with intellectual disability rely on the outerdirected approach even in more common situations in which they could perform well or at least accomplish what is expected without looking to others for cues as to how to behave. Bybee and Zigler (1992) highlighted this point with their finding that typically developing children used an outerdirected strategy in which they copied and otherwise looked to the experimenter's production of a picture using stickers for a novel or difficult task demand which they could not have otherwise fulfilled, whereas children with intellectual disability of the same MA used an outerdirected approach even on a simpler task that they should have been able to perform without external help (for a relevant review, see Bybee & Zigler, 1998).

The extent to which personality-motivational factors influence the lives of persons with intellectual disability, especially those with familial intellectual disability, is highlighted by findings that they are the best predictors of success and ability to integrate into mainstream aspects of society among persons within the range of mild intellectual disability (for reviews, see MacLean, 1997; Zigler & Hodapp, 1986). Consistent with the notion that mild intellectual impairment associated with familial intellectual disability simply reflects persons at the lower end of the natural continuum of the bell curve of intelligence, many persons in this grouping are able to hold jobs, live independently, and even start their own families (Bernheimer, Keogh, & Guthrie, 2006; Keogh et al., 2004; West, Wehman, & Wehman, 2005). As is the case with other persons, success is contingent primarily on extracognitive factors such as those related to personality and motivation (Merighi et al., 1990; Seltzer et al., 2009).

Although Zigler's (1967, 1969) initial broadening of the field of intellectual disability in the 1960s and 1970s to include extracognitive factors was focused almost solely on personality and motivational factors, it can be seen as the beginning of a more humanistic approach to research and scholarly understanding the whole person with intellectual disability. With the emphasis on the whole person, issues regarding the social and emotional lives of persons with intellectual disability became a priority for researchers, a timely occurrence in light of the relatively contemporaneous (and soon-to-follow) revelations of the atrocious conditions in which many persons with intellectual disability lived (e.g., in 1972, Geraldo Rivera exposed the conditions of the Willowbrook State School, a state-funded institution on Staten Island, New York, that housed 6,000 persons with intellectual disability) and the emergent emphasis on social adaptation in the essential (*DSM* and AAMD) diagnostic classification systems.

As with Zigler's other contributions to the developmental approach, the emphasis on personality and motivational factors and the whole person was expanded in many ways. The most notable is that Zigler's (1967, 1969) specific focus on these issues with regard to individuals with familial intellectual disability have since been applied to those with specific organic etiologies. Again, Cicchetti and colleagues provided early extensions of Zigler's dictum, as they focused on the temperament and socioemotional development specifically among children with Down syndrome (for extensive reviews, see Ciccheti & Beeghly, 1990; Cicchetti & Ganiban, 1990; Cicchett & Sroufe, 1978). This type of etiology-specific delineation is evidence of the advances in understanding the whole person in relation to essential issues that affect and are affected by development.

In this section, we highlight the advances and some of the difficulties in the specific study of three issues, social competence, language, and family relationships, that have been considered in relation to specific etiological groups and that reflect a commitment to understanding the social-emotional well-being of the whole person. Social competence represents the individual's abilities and

motivation to successfully interact in meaningful ways with others. Language reflects the case of a specific area of functioning that is essentially interrelated with social development. Family relationships involve issues of the reciprocal relationship between the presence of the child with intellectual disability and the family context. By disentangling these and related issues, we can better understand the transactions among the different systems that affect the whole person as well as between the individual and their immediate and broader systems (Bronfenbrenner, 1979). In the following sections, we consider the research on these components of the whole persons among individuals with the most commonly studied etiologies, Down syndrome, fragile X syndrome, Williams syndrome, and Prader-Willi syndrome.

Social Competence

Social competence is a key construct within the study of social development because it captures the dynamic relation between cognitive and social factors as they are applied to social adaptation (Iarocci, Yager, Rombough, & McGlaughlin, 2008). Although no operational definition of social competence is universally accepted, the term spans both socially adaptive behaviors as well as more basic social cognitive processes (Yager & Iarocci, 2013). It has been conceptualized as occurring at various levels of analysis—at the level of cognition (e.g., perspective-taking); overt behaviors/skills (e.g., use of eye contact); and outcome (e.g., social status, peer acceptance).

Developmental and contextual changes add further complexity to the study of social competence. It is both a developmental phenomenon that can be measured over the course of a child's development (i.e., ontogenesis) as well as a characteristic of a particular social encounter for which the time scale is in the order of seconds/minutes (i.e., microgenesis). Thus, continuities and discontinuities in the development of social competence are expected; children are better able to coordinate abilities and take advantage of resources with increasing age but may be less competent at certain developmental stages or in specific social contexts. What constitutes socially competent behavior changes depending on the age of the child as well as the context within which the child is evaluated (e.g., with parent or peers).

The same set of social skills are not available to the infant as they are to the adolescent. Thus, age-appropriate assessment in which the measure's focus is targeted to particular developmental periods are essential. For example, in infancy the quality of the parent–child interaction may be a particularly sensitive index of social competence as the interrelations between infant cues and parent sensitivity to the infant's cues improve the odds of survival as well as the social-emotional development of the infant. Peer interactions may be especially salient in middle childhood, whereas intimate relationships and community integration are paramount in adolescence.

In considering these aspects of social competence as well as other aspects of social development across populations, Yager and Iarocci (2013) note even persons with severe social impairment may be intensely aware of their social disconnectedness, experience distressing loneliness, and show a desire for greater social interaction. Accordingly, they emphasize that social motivation and social understanding may be relatively independent and measurable aspects of social competence. Within this framework, we use Rose-Krasnor's (1997) "prism model" to guide our understanding of the literature on social competence among persons with intellectual disability as it provides a useful framework for conceptualizing social competence and its levels of analysis. According to the model, social competence at a theoretical level is broadly defined as overall effectiveness in meeting short- and long-term social developmental needs/goals. Thus, social competence is viewed as a higher-order, organizing construct with transactional, context-dependent, and goal-specific characteristics. It cannot be reduced to any single index or skill but requires the active, skillful coordination of multiple processes as well as contextual factors to adequately meet the social demands of a particular situation (Iarocci, Yager, & Elfers, 2007; Iarocci, Yager, Rombough, & Mclaughlin, 2008). However, identifying and measuring a representative sampling of abilities/behaviors at the social motivation and skills level are useful in order to "tap into" the broader theoretical construct of social competence.

According to the prism model, social competence can be studied empirically at two distinct levels of analysis: the *index* level and the *motivation/skills* level (Rose-Krasnor, 1997). The index level represents real-life summary indicators of social competence (e.g., attachment security, peer acceptance, or employment success) that are considered to be situation/context-specific (e.g., with peers vs. with family). Although generally indicative of social competence, these indexes do not provide detailed information about the social presentation of an individual. Their utility in assessment is primarily as outcome measures or gross screening tools (e.g., identifying individuals who may be socially impaired). The *motivation/skills* level is comprised of the underlying dispositions and abilities that provide the "building blocks" of social interactions (e.g., social

motivations and social skills). Social skills include both social-cognitive abilities (e.g., perception and processing of social stimuli) and the more overt, observable social behaviors (e.g., eye contact, conversation ability). Any given social motivation or skill may be relevant across contexts or prove particularly valuable within a specific social context. In general, social motivations and skills tend to be more accessible to assessment methods (as compared with the indexes) and are commonly measured with performance-based laboratory tasks (e.g., tests of emotion recognition) or observation-based rating scales.

In this brief review of research on social competence among specific etiological groups of persons with intellectual disability, we include studies that are focused on the index level and those that are focused on the motivation/skills level. At the index level, the studies provide information about the individual's social behavior for adaptation, whereas those at the motivation/skills level contribute to an understanding of the socio-cognitive processes that underpin social behaviors.

Social Competence Among Persons With Fragile X Syndrome

Children with fragile X are often diagnosed with ADHD as they show poor attention span, impulsivity, and high motor activity. With age, hyperactivity and impulsivity subside yet attention deficits and inhibitory control problems persist (Cornish et al., 2008). High rates of autism spectrum disorder are also noted in this group along with considerable overlap of symptoms, although those with fragile X and autism display significantly less impairment on measurements of social response on the Autism Diagnostic Observation Schedule (ADOS), including the areas of Response to Joint Attention, Responsive Social Smile, and Facial Expressions (Wolf et al., 2012). For example, children with fragile X tend to show gaze avoidance, hyperarousal, repetitive activity, and motor stereotypy. Expressive language deficits are also common and include perseverative speech, echolalia, self-talking, and cluttering (Fletcher et al., 2007). Children with fragile X are also shy and at higher risk of developing social anxiety (Teisl, Reiss, & Mazzocco, 1999).

At the Index level, individuals with fragile X show relatively good adaptive skills and many are able to engage in occupational activities (Fletcher et al., 2007). However, they continue to show problems with temper outbursts as well as obsessional and aggressive behaviors well into adulthood (Howlin & Udwin, 2002).

At the motivation/skills level, children with fragile X are reported to show less approach, persistence, and adaptability in social interactions. Individuals with fragile X are described as socially anxious and withdrawn, and tend to avoid eye contact and have limited interaction with peers (Cornish et al. 2001; Kaufmann et al. 2004). In an analysis of scores on the Autism Diagnostic Observation Schedule (ADOS), Wolf et al. (2012) found that participants with both fragile X and autism were capable of appropriately responding to social bids made by others as indicated by their performance on the subtests of Responsive Social Smiling, Facial Expressions, Response to Joint Attention, but showed poor social initiative as indexed by the of Showing, Requesting, and Initiation of Joint Attention. Accordingly, Wolf et al. (2012) argued that the social difficulty in fragile X has more to do with a lack of prosocial initiative rather than any lack or impairment of social ability or social awareness. They speculated that the lack of initiative in making social bids was likely related to the high level of social anxiety in this group.

Initial evidence regarding the processing of emotions, faces, and other social information among persons with fragile X underscores the importance of considering developmental level, rather than CA, as patterns of performance which appear to reflect universal impairments or differences in relation to that of same-aged peers are considerably more nuanced in relation to MA-appropriate levels. For example, Shaw and Porter (2013) found that participants with fragile X (mean CA of 24.8 years and mean MA of 8.4 years) displayed specific emotion recognition deficits for angry and neutral, but not happy or fearful, faces as compared with both MA-matched (mean MA of 9.2 years) and CA-matched (mean CA of 24.5 years) typically developing persons, but developmentally appropriate visual scanning of emotional faces. Although the participants with fragile X displayed reduced attention to the eyes and different visual scan patterns of emotional faces as compared with the CA-matched typically developing individuals, their scanning patterns were commensurate with those of the MA-matched typically developing participants. The complexity in the relation between behavior and processes is highlighted by Hagan, Hoeft, Mackey, Mobbs, and Reiss's (2008) finding that 10 high-functioning females with the fragile X full mutation (mean CA of 16.4 years and IQ of 91) as compared with 10 typically developing girls matched on age but not IQ (mean CA of 15.2 and mean IQ of 106) showed intact emotion recognition despite a potentially disrupted neural circuit that modulates emotional responses to faces even when differences in IQ and accuracy of responses were statistically controlled. In a related study of visual scan paths, Williams, Porter, and Langdon (2013) found that

participants with fragile X (mean CA of 23 years and MA of 8.7 years) generally attended to social information overall to a similar degree as MA- (mean MA of 8.7 years) and CA- (mean CA of 23.2 years) matched typically developing participants, but were faster to disengage their attention away from social information in naturalistic static social scenes as compared with these groups as well as with a group of participants with Williams syndrome. Williams et al. concluded that the faster disengagement of attention away from social information was evidence of the avoidance of social stimuli among persons with fragile X.

In a study of higher order skills relevant to social understanding, Losh et al. (2012) examined theory of mind and pragmatic language skills among boys with fragile X-only, boys with fragile X and autism, boys with autism only, boys with Down syndrome, and typically developing boys. They found that both the participants with autism-only and the participants with both fragile X and autism performed most poorly, whereas the boys with fragile X-only did not differ significantly from the group of boys with Down syndrome or the MA-matched typically developing boys. Moreover, for all the groups, better theory of mind scores were associated with more pragmatic language competence as indexed by the Pragmatic Judgment subtest of the Comprehensive Assessment of Spoken Language. Losh et al.'s conclusion that the boys with fragile X-only showed relative strengths in theory of mind and pragmatic language and therefore that the deficits in these areas may be specific to those with both fragile X and autism highlights the social differences between the two subgroups of fragile X and suggests that any social problems associated with fragile X per se are not likely associated with higher-order cognition.

In summary of the work on social competence among persons with fragile X, the few preliminary studies on index level suggest good adaptive and occupational skills, but also behavioral problems that may interfere with overall social adjustment. At the motivational/skills level, social avoidance and anxiety appear prominent, yet unusual social attention processing is also present. Preliminary, but complex, profiles of both age-appropriate and impaired emotion recognition and theory of mind emerged, depending on what was being measured and with what task. Difficulties with theory of mind and pragmatic language tasks were specifically associated with fragile X, but only when co-occurring with autism.

Social Competence Among Persons With Down Syndrome

Children with Down syndrome typically fare better than children with other etiologies with regard to certain aspects of social competence. For example, at the index level they show generally good social adaptation and positive social outcomes (Rosner, Hodapp, Fidler, Sagan, & Dykens, 2004), whereas the profile is mixed at the motivation/skills level. Rosner et al. (2004) studied 177 persons with intellectual disability aged 4–49 years and found that the number and quality of social activities and relationships as measured by the Child Behavior Check List (CBCL; Achenbach, 1991) was significantly better among participants with Down syndrome compared with groups of children with Prader-Willi and Williams syndrome, after both age and IQ were covaried in all between-group analyses to account for the fact that the participants with Down syndrome were approximately 4–5 years younger and 12–16 points lower in IQ than the other two groups. In particular, the children and youth with Down syndrome were reported to behave well with others, show involvement in organizations, and demonstrate good job skills. In apparent contrast, Guralnick, Connor, and Johnson (2009) focused on more fine-grained analyses of peer social contacts, networks, quality of play, degree of control of play, and the characteristics of playmates, and found fewer well-developed peer networks in comparison to a MA-matched group of typically developing children. Specific areas of difficulties noted were the children's level of involvement in play with peers, linkages to other settings (e.g., school), and control of play. The seeming inconsistencies between the studies simply highlight two essential methodological points—the type of measure (global vs. fine grained) and the comparison group (typically developing vs. developmental disabled) need to be considered when interpreting findings.

With regard to the motivation/skills level, despite evidence of relatively good motivation and interest (e.g., face gazing and smiling behaviors) (Moore, Oates, Hobson, & Goodwin, 2002), difficulties have been noted in aspects of social cognition such as joint attention and theory of mind as compared with both MA matched typically developing children and children with nonspecific intellectual disabilities (for a review, see Iarocci et al., 2008). Children with Down syndrome were found to show fewer social referencing looks to their mothers in ambiguous situations (Kasari, Freeman, Mundy, & Sigman, 1995b) and make fewer attempts to direct their mother's attention across social situations (Fischer, 1987; Landry, Garner, Pirie, & Swank, 1994). Concordantly, Fidler (2005) found that toddlers with Down syndrome showed fewer nonverbal, instrumental requests than did typically developing and developmentally disabled toddlers matched on MA

and that these requests were related to the level of their problem-solving abilities.

Children with Down syndrome appear to show poorer emotion recognition relative to their cognitive abilities (Kasari, Freeman & Hughes, 2001; Kasari, Freeman & Bass, 2003), and appear to have particular difficulties with identifying and labeling fear and anger (Kasari & Freeman, 2001). Even when language demands were minimized with the use of nonverbal photo matching of expressions, Williams et al. (2005) found that children with Down syndrome had difficulty with fearful expressions. Concordantly, Wishart et al. (2007) found that persons with Down syndrome were particularly impaired on matching fearful expressions as compared with individuals with fragile X syndrome, those with nonspecific intellectual disability, and typically developing children. In addition to the difficulties recognizing emotions in others, children with Down syndrome have been found to show decreased emotional expressiveness. Early in infancy, they appear to have dampened smiles, shorter and less frequent displays of emotion, and longer delays to express emotion as compared with typically developing children (Emde & Brown, 1978; Thompson et al., 1985). Jahromi, Gulsrud, and Kasari (2008) found that children with Down syndrome generally showed more negative affect and difficulty regulating their emotions during challenging tasks as compared with typically developing children. The children with Down syndrome seemed to have a limited repertoire of behaviors to cope with frustration and, in fact, displayed more frustration and fewer cognitive self-soothing techniques. Consistent with the notion that personality-motivational characteristics can interfere with optimal performance among persons with intellectual disability, the children with Down syndrome oriented more to the experimenter without asking for help.

Despite the apparent difficulties in emotion recognition, expressivity and regulation, children with Down syndrome generally show more responsiveness to others (e.g., comforting) during distressing situations as compared with typically developing children. Although Kasari et al. (2003) found a poorer understanding of the concept of empathy among persons with Down syndrome, they reported an awareness of situations that are potentially distressing to others and the commission of appropriate actions to comfort others.

In adolescence and early adulthood, individuals with Down syndrome appear to become more withdrawn and show less pleasure or animation (Fletcher et al., 2007). The social withdrawal may be related to their higher risk of mental health problems such as the higher incidence of depressive disorder, anxiety, and obsessive compulsive disorder among the young adults (Dykens, Shah, Sagun, Beck, & King, 2002; Fletcher et al., 2007). Early onset Alzheimer's disease is also more likely in this group and possibly has adverse effects on social functioning (Prasher, Chung, Hague, 1998).

In summary, at the index level, children and youth with Down syndrome appear to show relative strengths in social competence as compared with other developmentally delayed youths. However, the type of measure and the comparison group need to be considered when interpreting as these findings of strengths may not be found in comparison to typically developing children. At the motivation/skills level, social motivation, interest, and responsiveness appear to be relative strengths, whereas social-cognitive abilities and emotion recognition, expressivity and regulation may be areas of relative weakness.

Social Competence Among Persons With Williams Syndrome

Children with Williams syndrome exhibit "hypersociability" and tend to be overly friendly, engaging, and responsive to others (Fidler, Hepburn, Most, Philofsky, & Rogers, 2007; Mervis et al., 2003). The social approach behavior appears to be compulsive since these children's approaches to strangers are typically indiscriminant even when the children have knowledge of the approachability of the other (Frigerio et al., 2006), and most report being scared of strangers (Dykens, 2003). Children with Williams syndrome show intense and prolonged attention to faces to the detriment of attention to other aspects of their environment (Mervis et al., 2003), yet their emotion recognition skills are delayed (Fidler et al., 2007; Gagliardi et al., 2003).

At the index level, individuals with Williams syndrome appear to show relative weaknesses in adaptive daily living skills (Hahn, Fidler & Hepburn, 2014; Mervis et al. 2001; Plissart et al. 1994), although they improve into adulthood (Howlin, Elison, Udwin, & Stinton, 2010). Howlin et al. used both cross-sectional and longitudinal designs and found no evidence of cognitive or linguistic deterioration overtime that could account for poor adaptive functioning among persons with Williams syndrome. Rather, adaptive functioning (as measured by the Vineland Adaptive Behavior Scales) generally improved until age 50 years. Specifically, Communication domain scores were consistently lower than scores in other domains and the relations between Socialization and Daily Living scores varied with age. However, parent reports suggest that these

individuals are dependent on family members and struggle with physical and mental health problems in adulthood. For example, 239 parents of adults (age 18–56 years) with Williams syndrome surveyed by Howlin and Udwin (2006) reported high rates of physical health problems as well as increases in rates of mental health problems (depression or anxiety) with age. Educational and employment attainments were generally low and self-help skills were relatively poor. Most (62%) of the adults with Williams syndrome were still living at home, some with quite elderly parents.

In Rosner et al.'s (2004) comparison of participants with Down syndrome, Williams syndrome, and Prader-Willi syndrome, those with Williams syndrome scored lower on social competency on the CBCL as compared with participants with Down syndrome, but higher as compared with participants with Prader-Willi syndrome. Most persons with Williams syndrome experienced difficulty with social interaction and were socially isolated (Davies et al., 1998). In one early study, 96% of all the individuals were described as experiencing difficulty in making friends and 76% were reported as having few to no friends (Udwin, 1990). With regard to occupational functioning, those with Williams syndrome scored lowest on job skills using the CBCL, which includes both household chores and jobs outside the home (Rosner et al., 2004). Problems with distractibility, social disinhibition and overfriendliness, as well as anxiety have also been noted (Davies et al., 1997; Udwin et al., 1998).

At the motivation/skills level, children with Williams syndrome have been found to show unusually intense social interest and processing of faces and eyes. For example, children with Williams syndrome fixate on faces longer than verbal IQ matched typically developing children and are slower to disengage their gaze once fixated on eyes (Porter et al., 2010) or a face (Riby et al., 2010). At an even more general level, Williams, Porter, and Langdon (2013) also reported difficulties disengaging attention rather than attentional capture among individuals with Williams syndrome, after they manipulated the location of socially salient information within visual scenes. These studies suggest that some aspect of selective attention may be impaired and implicated in the social perception behavior of children with Williams syndrome.

Despite the high social interest and intense attention to faces, individuals with Williams syndrome display significant impairments in recognizing emotions (Lacroix, Guidetti, Roge, & Reilly, 2009). Although they look longer at social stimuli they do not appear to process all relevant aspects but, rather, show a bias toward positive elements. In a study on autonomic responsiveness to emotionally laden images with social or nonsocial content, Plesa-Skwerer et al. (2011) found that the participants with Williams syndrome looked significantly longer at the social images as compared with images without social content and displayed reduced arousal to the negative social images as compared with the nonverbal MA-matched typically developing groups. Ironically, the awareness of emotional distress in others and heightened level of sensitivity to the emotional reactions of others (as evidenced by their high level of mimicry and imitation) does not appear to be applied to social decision making (Fidler et al., 2007).

Cognitive and language deficits seem to play a role in the social behavior of individuals with Williams syndrome. They appear to demonstrate difficulties in higher order social-cognitive functions such as atypical nonverbal communication, imagination, and problems in understanding the mental states of others (i.e., theory of mind; Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg, 2006; Tager-Flusberg & Sullivan, 2000). Generally, people with Williams syndrome show about the same level of performance on various theory of mind tasks as other children with developmental disabilities (Plesa-Skwerer & Tager-Flusberg, 2006). Tager-Flusberg and Sullivan suggested that theory of mind functioning among persons with Williams syndrome is characterized by relative sparing in the social-perceptual component, the ability to make an immediate judgment of a person's mental state, but impairment on the social-cognitive component. The social-pragmatic aspects of language (e.g., sensitivity of the communicative partner's perspective, nonverbal and verbal cues, and conversational reciprocity, interpreting jokes) are poor and similar to those of persons with autism (Klein-Tasman, Mervis, Lord, & Phillips, 2007; Stojanovik, 2006; Stojanovik & James, 2006).

The social approach behaviors of people with Williams syndrome may be due to a reduced ability to inhibit the urge to socially interact with others, suggesting a general rather than a social deficit in inhibition (Porter et al., 2007). For example, in examining the variability in the social approach behaviors of children with Williams syndrome ranging from 6 to 15 years of age with a cluster analysis, Little et al. (2013) identified social approach behavior subgroups and found that the response inhibition ability of the children was the strongest predictor of the social approach behavior profiles. Similarly, Kirk, Kocking, Rigby, and Cornish (2013) found that heightened anxiety in some individuals with Williams syndrome was associated with attention allocation away from the eye regions of threatening facial expressions, whereas attention to eye gaze is typically overly fixated and prolonged.

This finding suggests that anxiety may play a role in biasing social attention in at least a subset of individuals with Williams syndrome.

In sum, persons with Williams syndrome show problems in social competence at the index level as well as an unusual pattern of intense social interest and attention to social stimuli coupled with social-emotional, social-communicative, and cognitive deficits. This profile of high social interest and poor social information processing likely contributes to the poor social outcomes (e.g., social isolation) but also makes these individuals particularly socially vulnerable in a variety of ways (e.g., bullying, abuse). In addition, despite relatively stable cognitive and linguistic functioning, and general improvements with age on adaptive skills, individuals with Williams syndrome remain dependent on family members and struggle with physical and mental health problems in adulthood.

Social Competence Among Persons With Prader-Willi Syndrome

Individuals with Prader-Willi syndrome eat excessively (may also ingest inedible items) and are typically morbidly obese. The pursuit of food is so extreme that in many cases they will resort to risk-taking and antisocial behavior such as lying, stealing, and exchanging sexual favors for the promise of food. These individuals exhibit poor social judgment and difficulty with interpreting social cues (Koenig, Klin, & Shultz, 2004). Rituals, tantrums, skin picking, and compulsive behaviors, such as hoarding and placing objects in a certain order, occur at elevated rates among persons with Prader-Willi compared with persons with other etiological syndromes (Greaves, Prince, Evans, & Charman, 2006; Holland et al., 2003). Clinically, the rates of autism and mood disorders are also elevated (Vogels et al., 2004).

Prader-Willi syndrome is caused by missing paternal chromosome 15 (q11–q13 region). Seventy percent of the cases are due to the deletion (DEL) of the region in the paternal contribution, 25% of the cases to the duplication of the region in the maternal contribution, referred to as uniparental disomy (mUPD), and the rest to either a methylation imprinting defect or a translocation microdeletion (Ledbetter et al., 1981; Nicholls et al., 1989). Individuals with the DEL subtype are more severely impacted than those with mUPD in several domains, including the characteristic facial appearance and hypopigmentation (Cassidy, 1984), maladaptive behaviors (Dykens et al., 1999), and self-injurious behaviors (Symons et al., 1999). However, individuals with mUPD are at increased risk for developing psychosis after adolescence (Verhoeven & Tuinier, 2006) and autistic-like symptoms (Descheemaeker et al., 2006; Dimitropoulos & Schultz, 2007)

At the index level, based on parent ratings on the CBCL, children with Prader-Willi syndrome were reported to show poor behavior with others, and to be less active in social organizations compared with those with Down syndrome (Rosner et al., 2004). Their overall social competence did not improve with age as it did for children with Down syndrome and those with Williams syndrome (Rosner et al., 2004). Individuals with Prader-Willi syndrome also display poorer adaptive skills than would be expected given their intellectual functioning (Holland et al., 2003), and are reported by their caregivers to exhibit rigidity, inflexibility, and great difficulty with changes in their routines (Benarroch et al., 2007).

At the motivation/skills level, unusual but discrepant perceptual processing of faces was found in both genetic subtypes of Prader-Willi syndrome (Halit et al., 2008). In a preliminary neurophysiological study of individuals with Prader-Willi syndrome, an attenuated response to faces was found among eight individuals with paternal deletions (DEL), whereas the participants with mUPD showed a more typical neural response to faces although their eye gaze processing was similar to those participants with autism (Halit et al., 2008). Emotion recognition, a related area of social competence, is considered to be atypical in Prader-Willi, and may be related to high rates of comorbid affective psychosis (mUPD subtype) and clinical depression (DEL; Soni et al., 2008). Although Soni et al. (2008) found that caregivers drastically underestimated the emotion recognition and response abilities of both children and adults with Prader-Willi syndrome, problems in facial emotion recognition factors is thought to contribute to the peer relationship difficulties that are common among persons with Prader-Willi syndrome (Whittington & Holland, 2011). This is consistent with Tager-Flusberg et al.'s (1998) findings that adults with Prader-Willi syndrome performed significantly worse than adults with Williams syndrome when selecting the correct labels to match to the photographs of mental state expressions in the eye region.

Theory of mind also appears to be an area of impairment among persons with Prader-Willi syndrome. However, performance may vary with the type of task used or aspect of theory of mind that was measured. For example, Tager-Flusberg and Sullivan (2000) found that children with Prader-Willi syndrome (mean age 6 years, 11 months and mean IQ of 63) performed better on the false belief component of theory of mind than children with Williams Syndrome (mean age of 7 years 2 months

and mean IQ of 68). However, Koenig, Klin, and Schultz (2004) found that participants with Prader-Willi syndrome (mean age of 19.9 years and mean IQ of 67) performed as poorly as those with autism (mean age of 15.7 years and mean IQ of 69) and below IQ-matched participants without autism (mean age of 20.8 years and mean IQ of 72). The difficulties may be especially apparent when tasks require an appreciation for more abstract mental states as Koenig et al. used a social attribution task involving ambiguous stimuli (moving shapes in a video). In this context, the group with Prader-Willi syndrome made simple cognitive attributions about the moving shapes but were less able to make inferences about affective states related to the scenario (e.g., envy, jealousy), elements that were critical to understanding the social story.

Using within-group subtype analyses, Lo, Siemensma, Collin, and Hokken-Koelega (2013) found that both persons with the DEL and with mUPD subtypes showed poorer than expected performance on several components of theory of mind including first order belief, false belief, and second order false belief. In this group, 36% of children also met criteria for autism; 29% of the DEL and 41% of the mUPD subtypes. The most common symptoms of autism in the Prader-Willi syndrome group were in the area of maladaptive behaviors and routines such as interrupting conversations, talking to strangers, and making literal interpretations of expressions. Whereas most individuals with Prader-Willi syndrome do not exhibit the severity of symptoms found in autism, the social deficits that are reported appear to fall on the same continuum (e.g., poor social reciprocity and peer relationships).

Conclusions About Social Competence

The distinction between studies on index level, real-life summary indexes of social competence (e.g., peer acceptance, or employment success) and motivation/skills level, the underlying dispositions and abilities that provide the building blocks of social interactions (e.g., social motivations and social skills) is helpful to identify which aspects of social competence are impaired and the implications for overall adaptation. More of the research on social competence among the various etiological groups associated with intellectual disability has been focused at the motivational/skills level than at the index level and no studies were found that were focused on the relations between the foundational social abilities (e.g., face and emotion recognition) and real-life indexes of social competence (e.g., friendships). Understanding this relation will be informative about the extent to which current interventions, which are typically designed to tackle specific social processes such as face and emotion perception can impact real-life social adaptation with all its complexity and many components. Thus, intervention studies designed to specifically target face or emotion processing in children with ID should also include outcome measures of indices of real-world social competence, such as peer and family relations.

Comparisons across syndromes point to unique profiles of social competence that further underscore the notion of multiple sciences of different etiologies rather than a single monolithic one in the study of persons with intellectual disability. Patterns of differences and similarities in sociability across syndromes would help us understand the contribution that sociability has on the overall social outcomes of persons with specific syndromes and provide further insight into gene–brain–behavior systems. For example, the hypersociability in Williams syndrome is clearly an extreme phenotype of a critical aspect of social competence. With increasing methodological sophistication, even more detailed analyses of within group subtypes and variation allows for more nuanced and precise genetic associations and markers with sociability. All of these extensions of the research must begin to be considered within a developmental framework to account for changes across syndromes across the lifespan rather than being based on extrapolations from studies with limited ranges of CAs or MAs.

Language Development

As with many areas of functioning, early accounts of language abilities among persons with intellectual disability were consistent with the defect theories. Various impairments were forwarded as characteristic of all persons with intellectual disability, regardless of etiology, and were generalized to involve all facets of language. This outlook has since evolved largely in relation to the emergence of the developmental approach to intellectual disability and the concordant increased specificity in the ability to measure different aspects of language. Accordingly, the discussion around language abilities among persons with intellectual disability has been transformed to include issues of development and abilities, rather than just impairment, and an emphasis on the etiology-specific developmental profiles of the many different components of language functioning. However, as with other areas of functioning, this more fine-grained and comprehensive approach only allows for the relatively extensive study of the most common etiological groups, and the intermittent study of a few others. Furthermore, statements about a general language skill

are misguided, as language is a multi-faceted process in which children often display multiple divergent trajectories that are largely dependent on foci of the research and the measures that are used.

To provide some insight into the role of language in understanding the whole person, we provide a brief review of current thinking regarding the disparate profiles of language processing as well as their interplay with cognitive and social development among the most commonly studied etiological groups, those of persons with fragile X syndrome, Down syndrome, and Williams syndrome. We also review language among persons with Prader-Willi syndrome as an example of current thinking in research on less studied syndromes. As with virtually all areas of functioning, the available evidence is piecemeal with only some areas of language functioning being considered within each etiological group, and with little consistency in the foci of research across groups.

Language Development Among Persons With Fragile X

Among children with fragile X, language is generally reported to develop along a consistent trajectory commensurate with MA, with the exception of pragmatics (Abbeduto et al., 2012). Individual differences within the syndrome are also reported as a function of gender, as males tend to be more affected overall than females, and as a function of autism comorbidity (which occurs in 20–30% of cases; Hatton et al., 2006; Rogers, Wehner, & Hagerman, 2001). In other aspects, inconsistent evidence leads to questions about language development in this group. In one example, Roberts et al. (2002) reported that receptive vocabulary lagged behind expressive vocabulary in a group of young boys whose MAs ranged from 12 to 28 months (CAs 21 to 77 months), whereas Abbedutto et al. (2003) reported that receptive vocabulary was at nonverbal MA expectations in a group of male and female adolescents. These findings suggest either that the rate of vocabulary acquisition increases more quickly than the rate of general cognitive development among individuals with fragile X over the course of development or that comparing receptive to expressive vocabulary (Roberts, 2002) leads to a different interpretation of strengths and weaknesses than comparing receptive vocabulary to MA (Abbedutto et al., 2003).

In a longitudinal study of boys with a mean MA of 5-years at entry, Martin, Losh, Estigarribia, Sideris, and Roberts (2013) found parallel gains on the Comprehensive Assessment of Spoken Language (Carrow-Woolfolk, 1999) among those with fragile X without autism, fragile X with autism, and Down syndrome over a 3-year period. In all three groups, language appeared to be below non-verbal MA expectations, and both the boys with fragile X without autism and those with Down syndrome showed a pattern of vocabulary > pragmatics > syntax, whereas the boys with fragile X with autism showed a pattern of vocabulary > pragmatics = syntax due to poorer pragmatic performance in the comorbid autism group. Given the frequent reports of gender differences and consequential exclusion of females from many studies, the pattern of findings reported by Abbeduto et al. (2003), which were inconsistent with other studies, might be related to the inclusion of females in their study (Abbeduto et al., 2012). This was supported by findings from a longitudinal study of boys and girls with fragile X, in which Pierpont, Richmond, Abbeduto, Kover, and Brown (2011) found that phonological and verbal working memory predicted gains in vocabulary and syntax for boys, but not girls, with fragile X. The evidence from the study of language among individuals with fragile X highlights the importance of taking into consideration both gender and the presence of a comorbid diagnosis of an autism spectrum disorder in understanding the development of skills in this group.

Language Development Among Persons With Down Syndrome

In a review of language development from childhood to young adulthood among persons with Down syndrome, Chapman and Kay-Raining Bird (2012) note that children with Down syndrome display a specific phenotype of language learning, including uneven impairments in language skills, yet they are one of few etiological groups in which impairments in pragmatics (the social use of language) are not identified. Combining evidence from cross-sectional and longitudinal studies of language acquisition, Chapman and Kay-Raining Bird (2012) painted a picture of changes in language functioning across development. In early childhood, children with Down syndrome display deficits in expressive vocabulary that are below nonverbal MA expectations (Fidler, Hepburn & Rogers, 2006; Miller, 1995). However, from age 2 to 4 years, the rate of expressive vocabulary growth falls further and further behind both receptive vocabulary knowledge and nonverbal development (Miller, 1995), with receptive vocabulary remaining commensurate with non-verbal development until early adolescence (Chapman, Schwartz, & Kay-Raining Bird, 1991). As the grammatical complexity of language skills among typically developing children increases, children with Down syndrome appear to fall further and further behind, even as language skills continue to grow (albeit unevenly).

In an attempt to study the relationship between language and cognition among individuals with Down syndrome, Chapman, Hesketh, and Kistler (2002) conducted a 6-year longitudinal study of grammar in which they found that receptive syntax at the beginning of the study predicted later expressive syntax. Furthermore, short-term memory skills (both auditory and visual) predicted the rate of receptive syntax growth, which in turn predicted the rate of growth in Mean Length Utterance. Auditory short-term memory has also been implicated in phonological development (Kumin, Councill, & Goodman, 1994; Laws & Gunn, 2004), the emergence of which appears to be delayed among infants with Down syndrome, although the pattern has been reported to follow a typical trajectory (Smith & Stoel-Gammon, 1983).

Consistent with the developmental approach, Chapman and Kay-Raining Bird (2012) caution that the manner in which we measure development plays a role in our understanding of language-related strengths and weaknesses of individuals with Down syndrome, and could lead to an under-evaluation of abilities. For example, researchers debate the relative strength of receptive vocabulary among individuals with Down syndrome during adolescence, with Chapman et al. (1991) reporting that receptive vocabulary surpasses general MA, and others reporting that receptive vocabulary is below MA expectations (Hick, Botting, & Conti-Ramsden, 2005; Price, Roberts, Vandergrift, & Martin, 2007; Roberts, Hennon, et al., 2007). However, this discrepancy in findings may have more to do with the use of different MA measures across studies, rather than actually reflecting conflicting patters of findings. Further, with respect to grammar, when assessments of language are based on conversational samples (e.g., question–answer or spontaneous comments during free play), expressive syntax appears to reach a plateau in adolescence among individuals with Down syndrome (Chapman et al., 1998; Fowler, Gelman, & Gleitman, 1994). Conversely, when assessments of language are based on narrative samples, the development of expressive syntax continues through young adulthood (Chapman et al., 1998; Chapman et al., 2002; Thordardottir, Chapman, & Wagner, 2002).

Language Development Among Persons With Williams Syndrome

Some early accounts of individuals with Williams syndrome focused on apparent strengths in expressive language, to the extent that in an early account, Bellugi, Marks, Bihrle, and Sabo (1988) described them as demonstrating a double dissociation between language and cognition or as having intact language abilities despite a general level of functioning in the range of intellectual disability. However, Mervis (2012) and Karmiloff-Smith (1998, 2007) argue that the expressive language abilities of individuals with Williams syndrome only appear to be so outstanding when they are considered in relation to the extremely impaired skills, such as visuo-spatial construction, in this group. With closer scrutiny, various aspects of language also appear to be delayed or impaired, and the development of language appears to be interdependent with, rather than independent from, general cognitive development (Mervis, 2012).

Karmiloff-Smith et al. (1997) argue that the entire trajectory of language development is altered in Williams syndrome, and that this may be linked to the syndrome's characteristic hypersociability. Beginning in infancy, infants with Williams syndrome seem to pay excessive attention to people at the expense of joint attention behaviors, which are necessary precursors to typical language development (Bloom, 2002). Despite, or perhaps consequential to, their hypersociability, atypicalities have been reported in virtually all areas of pragmatic language abilities, which include language related to social interaction such as turn taking, modulating content for the audience, and communicating wants and needs (Philofsky, Fidler, & Hepburn, 2007). Specifically, individuals with Williams syndrome exhibit a particular pattern of unusual conversation that tends to include features such as excessive idioms, overfamiliarity, evaluative comments, and emphatic markers, a cocktail party speech that is partly responsible for the reputation of strong language (Mervis, 2012). Individuals with Williams syndrome are quite verbose, but this verbosity appears to mask difficulties in the social aspects of language, the very skill that was initially considered to be their primary strength.

Language Development Among Persons With Prader-Willi Syndrome

The difficulties in providing a comprehensive understanding of less common etiological groups are highlighted in the literature on the development of language among individuals with Prader-Willi syndrome. Impairments in both expressive and receptive language have been cited, with greater impairment reported in expressive language (Branson, 1981; Dimitropoulos, Ferranti, & Lemler, 2013; Kleppe, Katayama, Shipley, & Foushee, 1990; Munson-Davis, 1988), although these findings are plagued by methodological problems regarding the comparison groups. For example, findings that expressive language appears to be particularly problematic in individuals with Prader-Willi syndrome, with specific problems with

morphosyntax and possible difficulties with vocabulary and pragmatics (Van Borsal, Defloor, & Curfs, 2006) are compromised as they are framed only in relation to the expected norms for CA. Although preliminary, areas of strength in language abilities among individuals with Prader-Willi syndrome have also been suggested in phonology (Van Borsal et al., 2006) as well as in vocabulary knowledge and decoding in the domain of reading (Dykens, Hodapp, Walsh, & Nash, 1992).

The differentiation among subgroups within Prader-Willi provides an opportunity to better understand the relation between aspects of the disorder and those of language abilities, although the evidence is mixed. For example, Dimitropoulos et al. (2013) reported that participants with maternal uniparental disomy (mUPD) genetic subtype of Prader-Willi syndrome only show higher expressive language abilities relative to their receptive abilities, whereas Lewis, Freebairn, Heeger, and Cassidy (2002) reported no differences in speech or language between individuals with Prader-Willi syndrome from either deletion or maternal uniparental disomy. If researchers are able to cobble together a more comprehensive literature on language processing among persons with Prader-Willi despite the difficulties, the subtle differences between subtypes may be essential to understanding the genetic mechanisms of intellectual disability in this population and their relationships to language abilities.

Language, Cognition, and Socialization

Although some language skills appear to develop independently of other cognitive abilities in some etiologies, the interdependence of language, cognition, and socialization is evident (Chapman & Kay-Raining Bird, 2012), albeit in different ways across groups. For example, Mervis (2012) notes that intact verbal working memory is important for grammatical comprehension among children with Williams syndrome, more so than for typically developing children. Among individuals with Down syndrome, Kay-Raining Bird and Chapman (2012) highlight the interdependence of language in literacy development, as vocabulary comprehension is reported to be the best predictor of their literacy skills (Kay-Raining Bird, Cleave, White, Pike, & Helmkay, 2008).

Syndrome-specific patterns in language development may also play a role in the acquisition of other higher order cognitive skills, such as executive functions. For example, Campbell et al. (2013) found that verbal development, independent of nonverbal development, predicted cognitive flexibility among persons with Down syndrome (Campbell et al., 2013), and Landry, Russo, Dawkins, Zelazo, & Burack (2012) found that it predicted working memory as well as cognitive flexibility among both persons with Down syndrome and those with Williams syndrome. This type of quest to understand the interrelatedness among skills across development exemplifies an essential task of the developmental approach, but is not sufficient. Rather, in addition to psychologically measurable intrinsic factors which impact the development of language, the complexity of genetic and environmental factors and their interplay must be considered in relation to the development of unique profiles of language, or any other type of, skills specific to the etiological groups. This was highlighted by Kay-Raining Bird and Chapman (2012) who describe how school, SES, and the home environment can affect the development of literacy skills among children with Down syndrome. For example, individuals with Down syndrome raised in a home environment display higher reading scores than those raised in an institution (Bochner, Outhred, & Pieterse, 2001; Carr, 2000), and those in integrated school settings and from higher SES backgrounds also display better literacy skills (Bochner et al., 2001; Sloper, Cunningham, Turner, & Knussen, 1990).

In delineating that genetics must also be considered when studying the relations among socialization, the environment, and language abilities, Abbeduto et al. (2012) reviewed evidence of links between language skills in fragile X and levels of FRMP, the protein produced by the FMR1 gene that plays a critical role in synapse maturation and functioning. Specifically, levels of FRMP are reported to be related to communication scores, verbal IQ, and story comprehension (Bailey, Hatton, Tassone, Skinner, & Taylor, 2001; Kuo, Reiss, Freund, & Huffman, 2002; Simon, Keenan, Pennington, Taylor, & Hagerman, 2001). Yet interactions with parents also affect the development of language skills in children with fragile X. For example, maternal responsivity is reported to be associated with communication in children with fragile X (Warren, Brady, Sterling, Fleming, & Marquis, 2010). Specifically, Warren et al. (2010) reported that level of maternal responsivity was related to the rate of total communication, receptive and expressive language development in 36-month-old infants with fragile X syndrome. These types of findings regarding the influence of parents underscore Abbeduto et al.'s call for an increased consideration of the complex role of genetics in language development. For example, mother carriers with the full or premutation of FMR1 gene may themselves experience cognitive deficits or affective disorders, which may inadvertently contribute detrimentally to their children's language development (Abbeduto et al., 2012).

The Impact of a Child With Intellectual Disability on the Family

Consistent with the notion of understanding the whole person, the study of aspects of development that are intrinsic to the individual need to be supplements with regard to the study of family relationships. At every moment, the unique development of the child influences the signals that he or she sends out to the world. Beginning with the simple characteristics in temperament, the child demands more or less attention from the caregiver, which may be easily accommodated or may stretch the limits of the caregiver. The caregiver then approaches the child with a positivity or negativity that is in part influenced by the child. For example, consistent with the notion that children with Down syndrome have the reputation of being easy babies, the caregivers of children with Down syndrome report lower levels of stress than caregivers of children with other diagnoses such as autism (Dabrowska & Pisula, 2010) and Prader-Willi syndrome (Lanfranchi & Vianello, 2012). This easier personality likely leads to more positive interactions with parents and siblings.

These findings highlight that, as with all persons, persons with intellectual disability both affect and are affected by the close relationships in their lives, such as those with family members. Clearly, having a child with intellectual disability can uniquely impact the well-being of parents, siblings, and the family as a whole. Just as obviously, different etiologies can be associated differentially with family well-being since differences in development and symptomology may exert different types of stressors on parents and may also affect the availably of certain resources or coping mechanisms. This effect is transactional, since the impact on parental, sibling, and family well-being continually shape parenting techniques and other factors which are, in turn, impacting the well-being of the child, all within the context of the larger, community, and society in which the child and family reside.

Negative Emotional Outcomes for Parents of Children With Intellectual Disability

Not surprisingly, having a child with intellectual disability can impose a negative emotional toll on parents. Depression has been the most common negative outcome studied in parents of children with intellectual disability (Glidden, 2012), which appears to diminish with time. High rates of parental depression are more often reported soon after the birth of a child with intellectual disability relative to years later during childhood and adolescence (Glidden & Jobe, 2006; Glidden & Schoolcraft, 2003; Keogh, Garnier, Bernheimer, & Gallimore, 2000; Singer, 2006). Anxiety, pessimism, and anger have also been reported (Glidden, 2012; Hall, Bobrow, & Marteau, 2000; Hodapp, Dykens, & Masino, 1997). These reactions are often in reaction to specific aspects of the child's specific condition. For example, increases in pessimism in parents are correlated with increases in maladaptive behavior in children with Smith-Magenis syndrome (Hodapp, Fidler, & Smith, 1998) and with Prader-Willi syndrome (Hodapp, Dykens, & Masino, 1997).

In addition to the negative emotional impact that having a child with intellectual disability has on the parents individually, it has also been reported to negatively affect the parental dyad (Glidden, 2012). Having a child with intellectual disability has been reported to slightly decrease marital adjustment (Risdal & Singer, 2004) and increase divorce rate (Reichman, Corman, & Noonan, 2004), although Hodapp (2007) reported a lower divorce rate for parents of children with Down syndrome relative to parents of typically developing children thereby indicating that the specific developmental profile of children with Down syndrome may uniquely protect against negative marital outcomes. Marital outcomes among parents of children with intellectual disability have been reported to be related to paternal involvement (Simmerman, Blancher, & Baker, 2001; Willoughby & Glidden, 1995), with more marital satisfaction reported in couples in which the father is involved in caring for the child (Willoughby & Glidden, 1995) or at least perceived by the mother as being involved (Simmerman, Blancher, & Baker, 2001). Coping style is also related to marital satisfaction among parents of children with intellectual disability. For example, the use of problem-focused coping by both parents in dealing with hassles has also been found to be related to higher marital adjustment (Stoneman & Gavidia-Payne, 2006).

Positive Outcomes for Parents of Children With Intellectual Disability

Despite the challenges often associated with raising a child with intellectual disability, many of the same positive life changes and emotions such as love, joy, and satisfaction that are experienced by parents of typically developing children are also reported anecdotally and in qualitative reports by parents of children with intellectual disability (see Hastings & Taunt, 2002). For example, Flahery and Glidden (2000) reported that lower levels of depression, positive marital adjustment, and increased family strength were found in both adoptive and non-adoptive parents of children with intellectual disability. In addition, mothers and fathers who felt optimism, contentment, and happiness

also had less stress and better family adjustment (Trute & Hiebert-Murphy, 2005).

Predictors of Parental Outcome

The stress of receiving a diagnosis is one factor often reported to elicit negative reactions and elicit symptoms of depression in parents soon after the birth of a child with intellectual disability (Glidden & Jobe, 2006, 2009; Glidden & Schoolcraft, 2003; Poehlmann, Clements, Abbeduto, & Farsad, 2005). Although this certainly can take an emotional toll, not receiving a specific diagnosis can be just as distressing for a family with a child who is not developing at the same rate as his/her peers (Glidden, 2012). A difference in the timing of when parents receive their child's diagnosis is thus one factor that has been reported to affect positive or negative outcomes depending on the etiology of the intellectual disability (Lenhard, Breitenback, Ebert, Schindelhauer-Deutscher, & Henn, 2005; Poehlmann et al., 2005). Specifically, parents report less anxiety, worry, and regret (Lenhard et al., 2005), and even relief (Poehlmann et al., 2005) when their children receive a diagnosis. Concordantly, Al-Yagon and Margalit (2012) highlight that early knowledge of a diagnosis was related to better parental adjustment among parents of children with Down syndrome. This is exemplified by findings that parents of children with Down syndrome generally show levels of anxiety, depression, and parental stress that are similar to those of parents of typically developing children (Hall, Bobrow, & Marteau, 2000), but not when they received a false negative diagnosis during prenatal screening (Hall & Marteau, 2003). In those situations, they display high levels of parenting stress, a negative attitude toward their child, and worse overall adjustment.

The type of coping mechanisms that are used and their availability to the parents also have been found to predict family well-being. Coping strategies that are focused more on problem solving and social support are related to more positive emotional outcomes than those using denial escape or avoidance of difficulties (Altshuler & Ruble, 1989; Levy-Shiff, Dimitrovsky, Shulman, & Har-Even, 1998; Reichman, Miller, Gordon, & Hendricks-Munoz, 2000). For example, mothers who use escape avoidance coping have been found to report higher levels of depression, whereas mothers who employ positive reappraisal report higher levels of subjective well-being (Glidden et al., 2006). Gender differences in coping styles have also been reported, as mothers tend to seek more emotional support whereas fathers seek more instrumental support and problem solving (Sullivan, 2002).

The children themselves, and especially their behaviors, impact considerably on parental well-being (Glidden 2012), as increases in child behavior problems are reported to contribute to more negative parental outcomes than the diagnosis of intellectual disability itself (Baker et al., 2002, 2003). Consistent with the findings that parents of children with Down syndrome experience a relative advantage as compared with parents of children with other etiologies, Al-Yagon and Margalit (2012) suggest that less severe behavior problems in children with Down syndrome may contribute to more positive outcomes for their families since less stress is associated with getting such behaviors under control.

Dyadic Interaction Between Mothers and Children With Intellectual Disability

One contributor to the parents' level of well-being that is affected by the child with intellectual disability is the parent–child dyad with that child. As with other aspects of social development and the family structure, the impact must be considered in relation to the relevant construct, task, and etiology (Hauser-Cram, Howell-Moneta, & Mercer-Young, 2012). In one example of an etiology-specific finding, Vaughn, Goldberg, Atkinson, Marcovitch, MacGregor, and Seifer (1994) found that young children with Down syndrome display an unclassified insecure attachment style relative to typically developing children who generally show a secure attachment to their mothers, as they are less reactive to their mothers and seek their mothers less for reassurance upon return. Esbensen et al. (2012) suggest that, in addition to deficits in cognitive functioning, the increase in the unclassified insecure attachment style among children with Down syndrome relative to typically developing children may be due to etiology-specific characteristics of Down syndrome that put strain on the mother–child relationship. Characteristics such as congenial heart defects, thyroid dysfunction and sleep problems, and ear infections can all limit the energy of children with Down syndrome and their ability to engage in sustained interactions with their mothers. Children with Williams syndrome display a similar attachment style as they show less intense facial and vocal distress when their parents leave the room and need less consoling upon being reunited with parents (Jones et al., 2000).

Mother–child interactions illustrate the etiology specific effects on parenting style. For example, parents of children with Williams syndrome were found to use more task directives than parents of children with Prader-Willi syndrome when playing with a puzzle, a style apparently adopted due to their childrens' poorer spatial skills (Ly &

Hodapp, 2005). In addition, the unique hypersocial personality style of children with Williams syndrome can be both beneficial and detrimental to the relationship (Jones et al., 2000). Accurate recognition of positive emotions creates a synergy of positive bi-directional affects in the dyad, although extensive interactions with others may diminish the child's interactions and relationship with their own mother (Järvinen-Pasley et al., 2008; Laing et al., 2002). With regard to Down syndrome, infants and toddlers appear to show less coordinated shared attention with their mothers as compared with typically developing children matched on MA (Legerstee & Fisher, 2008).

In keeping with Zigler's (1967; Zigler & Hodapp, 1986) argument for considering the ways that being a person with intellectual disability inevitably involves life experiences that affect the ways that people behave and perform in all aspects of their lives, the areas of social competence, language development, and family relationships are all essential to real lives lived. The simple cataloguing of the phenotypes as though the genotype is the only contributing factor to the eventual developmental path is clearly an erroneous strategy as features of different phenotypes present particular challenges for optimal functioning and relating within the context of the whole person in his or her family and environment.

NEUROSCIENCE AND THE DEVELOPMENTAL APPROACH: BENEFITS AND PITFALLS IN THE APPLICATION OF CUTTING-EDGE TECHNOLOGY

The advance of technology and the increase in the number of researchers who have access to cutting-edge tools like functional magnetic resonance imaging (fMRI), event-related potentials (ERPs), and magnetoencephalography (MEG) have led to a growing number of studies that involve mapping the relations between how an individual performs on a task and the brain regions that support that performance. The potential utility of these increasingly sophisticated and precise technologies along with the concomitant theoretical and methodological contributions of the field of neuroscience provide promise for yet a new stage in the development of the developmental approach to the study of persons with intellectual disability. Concordantly, as neuroscientists begin to delve into the study of intellectual disability, the history of the developmental approach can guide them in detecting theoretical and methodological landmines to avoid and directions of promise to pursue.

A Primer on What fMRI and ERP Measure

The study of brain function, which reflects modern techniques for linking behavior to brain, has generally involved either fMRI or ERP technology. Briefly, fMRI is based on the basic principle that any given region of the brain that is actively engaged in a task will draw more blood. This blood, rich in oxygen, is detected magnetically due to its iron content. fMRI is used to measure the so-called blood-oxygenated dependent level (BOLD) response, which serves as an indirect marker of neuronal activation during a cognitive operation. Namely, neural firing increases in a particular brain area as it is being engaged, which leads to both greater blood flow and release of oxygen to this area to satisfy local metabolic demands. By contrasting experimental conditions that differ only in the cognitive construct one is measuring or by comparing task based activations to rest, researchers can isolate the location of brain activity specific to a particular task or cognitive process. The major advantage of fMRI is that it has exquisite spatial resolution, allowing scientists to locate the specific areas of the brain that underlie task performance with millimeter precision. One of the disadvantages is that, because blood flow changes occur slowly, the temporal resolution of fMRI is on the order of seconds, which is much slower than the timing of brain processing in general, which is in the order of milliseconds.

In contrast to fMRI, event-related potentials (ERPs), offers the fine-grained temporal resolution researchers seek, but at the expense of spatial resolution. In order to relate brain activity to specific processes and behaviors, researchers isolate the continuous, ongoing electrical activity of the brain as measured by encephalography (EEG) into segments that are time-locked to a specific stimulus (Luck, 2005). ERPs display a stable time relationship to a discrete event (Luck, 2005). Because ERPs are small in size relative to other physiological events, many presentations of the evoking stimuli are necessary to average out the potentially unrelated events (Luck, 2005). For example, if a tone is played, the brain responds to that tone, but it also responds to other things that are present in the environment at that same time such as how a person is feeling, what they are looking at, and what they are thinking about. By time locking the physiological response to the presentation of the tone, and presenting the tone repeatedly, we can reduce the noise (the brain's response to things other than the tone) and extrapolate the brain's specific response to the tone itself (Luck, 2005). The brain's responses to a stimulus generate an ERP response that has specific peaks and troughs whose amplitude (height)

and latency (timing) can be compared either between conditions or between groups. The nomenclature of ERPs is based on the direction (positive or negative from 0) and time post stimulus onset, such that a P100 (or P1) represents a positive peak occurring 100ms post stimulus and an N170 represents a negative peak that occurs 170ms post stimulus. The meaning of each of these components have been isolated (with considerable disagreement) to reflect perceptual, attentional, or cognitive mechanisms and the stimulus factors to which they are sensitive.

An ERP represents only a sample of the electrical activity that is present in the brain when a specific event occurs (Luck, 2005). Since electrodes are located at the surface of the scalp, the activity of one single neuron is too small (and too far away) to record. Thus, ERPs are used to measure the integrated activity of many neurons that are recorded at the surface of the scalp. Specifically, neurons must have their dendritic trees oriented to one side (Coles, Gratton, Kramer & Miller, 1986) to be measured. ERPs are generally thought to reflect postsynaptic potentials (Luck, 2005) because these occur in the dendrites essentially instantaneously, while action potentials need to travel down the axon of a neuron (Coles et al., 1986; Luck, 2005). The advantage of this technique is that its temporal resolution is in the order of milliseconds, which reflects the speed with which our brain processes information. This allows researchers to examine different levels of processing such as perception and cognition by looking at early (first 250ms or so) and late (after 300ms) time frames of processing, which can reflect afferent (receiving input) or efferent (sending output) neural pathways. The disadvantage of ERPs is that because electrodes are placed at the surface of the scalp, which is far from the brain, the spatial resolution of ERPs is poor. Thus, fMRI is best suited to tell us *where* in the brain things happen, whereas ERPs allow us to know *when* things happen.

Neuroscience and the Developmental Approach: A Messy Meeting of Disciplines

The lessons learned from the developmental approach to intellectual disability which are particularly relevant to the emergence of the study of intellectual disability from a neuroscience perspective relate primarily to matching issues. One, comparing individuals with an intellectual disability to typically developing individuals who have normal cognitive function is problematic because it confounds general cognitive deficits with any specific skill or process being measured. Two, when matching on the basis of MA, the composition of the comparison group is particularly important and should be homogeneous (e.g., Down syndrome) as opposed to mixed (i.e., participants from different groups) such that (1) direct comparisons can be made between two groups that differ in only the cause of their intellectual disability, and (2) researchers can replicate findings by having similarly composed comparison groups. As will become evident from the review of studies that follow, these lessons, which form the basic tenets of the developmental approach to intellectual disability, are often ignored in studies of intellectual disability in which fMRI or ERP technology are used.

Generally, when reviewing studies on intellectual disability within the context of the developmental approach, papers in which the performance of individuals with intellectual disability are matched to the CAs of typically developing participants are discounted since performance differences are simply attributable to the a priori differences in level of functioning between the groups, reflecting the defect, rather than the developmental, approach. However, the notion of how best to apply the developmental approach to the study of brain processes still needs to be considered. For example, in the absence of a cognitively demanding task in which age-related differences would be expected, do we expect the neuroanatomical substrates (in the case of fMRI) or the neurophysiological components (in the case of ERPs) engaged or elicited by the presence of a stimulus to reflect physical or mental maturity? Would patterns of brain activation of a 12-year-old individual with Down syndrome whose MA is 6 resemble that of a 12-year-old or that of a 6-year-old, or somewhere in between? Does this vary as a function of the level of intellectual impairment? Is the answer to this question diagnosis-dependent? Task dependent? Answers to these questions will help to define and refine the reciprocal relationship, not only between typical and atypical development but also between developmental psychopathology and neuroscience.

Neuroscience and Intellectual Disability

As applied to the study of intellectual disability, the study of neurophysiology and neuroimaging are in their infancy. In applying the developmental approach to assessing the contributions of neuroscience (broadly speaking) research in the study of intellectual disability, we review all of the research studies that we could find in which functional magnetic resonance imaging or event-related potentials were the primary methodological tool. Consistent with the developmental approach, the discussion of these articles will be focused on both the main findings from these studies and how they contribute to our understanding of both

persons with intellectual disability and of typically developing persons, but also the implications of matching or non-matching practices for these findings and subsequently on advancing the field. Studies were selected for review according to the following course of action. An advanced PubMed search of the most common genetic disorders associated with intellectual disability—Down syndrome, Williams syndrome, fragile X, and Prader-Willi—was conducted with either the terms *event-related potentials* or *functional magnetic resonance imaging*. In addition, we looked through the reference sections of the articles generated through our original search and added additional relevant articles. This extended search yielded a total of 49 published research studies, 35 of which were studies that involved fMRI technology and 14 that involved ERPs as their main methodological tool. Abstracts of these studies were then read to exclude reviews and other non-empirical papers ($n = 6$), or papers that were irrelevant to perception, attention, and cognition very broadly defined (e.g., articles whose primary focus was on Alzheimer's disorder among persons with Down syndrome, or those looking at resting state fMRI were rejected; $n = 12$), or those for which full text articles could not be located ($n = 3$). This left a total of 28 articles that are reviewed here. The details of each study, including the chronological and mental ages of participants, and the matching strategies used by researchers are presented in Table 1.1, and are sorted as a function of etiology. Though the matching strategies used by researchers will be highlighted in the text, we refer the reader to the table for the specific participant and matching characteristics. Also included in the table are the relevant methodological factors, and the main research findings.

As the application of neuroscience techniques to the field of intellectual disability is nascent, we found little consistency in findings, or even in areas of study. The themes of sociability and food-related preferences represent the majority of areas of inquiry in the study of individuals with Williams and Prader-Willi syndromes respectively as these areas represent such consistent aspects of the phenotype for both of these disorders. However, no such consistency is to be noted across other areas of intellectual disability. Accordingly, few studies are replicated and no firm conclusions can be drawn regarding areas of strength or weakness or areas of the brain that are over or under active in response to specific types of stimuli. Although the main findings across studies will be reviewed, the main focus of this review is on the relationship between findings and the developmental approach to intellectual disability as it applies to neuroscience.

Matching in Neuroscience Studies. When reviewing the different studies, three broad matching classifications were used. The first category included studies with CA-matching alone. The majority of the studies ($n = 19$) fell under this umbrella of problematic methodology. The second category of studies ($n = 8$) involved the consideration of developmental level either directly with matching mental age or statistically by covarying IQ in the analyses. Finally, one study involved matching on a specific aspect of functioning (temperament) to assess the specificity of social approach among persons with Williams syndrome.

The publication of these papers in high-impact journals, despite the omission of any mention of such foundational issues in the developmental approach as the role of discrepant IQs or level of functioning, is particularly troubling. Conversely, many developmentalists are beginning to conduct research using cutting-edge technology without the necessary background training. As such, basic conventions in the ERP and fMRI literatures regarding methodology, such as compensating for multiple comparisons in fMRI and testing for assumptions underlying statistical tests such as sphericity in ERP data, which are common knowledge among basic neuroscientists in the field and essential to the acceptance for publication are often overlooked. One explanation is that due to the amount of effort required to develop meaningful tasks that can be completed by atypical populations and the difficulty involved in recruitment and testing, some of the methodological rigor of basic science papers gets overlooked (for information about basic considerations in fMRI research, see Bennett, Wolford, & Miller, 2009; Bennett, Baird, Miller, & Wolford, 2010; for considerations related to ERPs, see Picton et al., 2000). We review the available etiology-specific neuroscience-type studies within the context of the basic fundamentals of both the developmental approach and cutting-edge technologies.

Persons With Fragile X Syndrome. Due to the gender differences associated with the presence of an unaffected, protective X chromosome among females with fragile X syndrome, males and females are generally studied separately. Differences in their cognitive phenotypes are commonly associated with the lack of intellectual impairments noted among females with fragile X. We identified 10 neuroscience-based studies of fragile X, half of which involved fMRI to assess various aspects of functioning that included cognitive interference via the Stroop task, auditory discrimination, and emotional identification among females with fragile X, and the detection of eye gaze direction and inhibition using a go/no-go task among males, and

TABLE 1.1 Summary of Studies Using Neuroscience Tools Among Individuals With Developmental Disabilities

Citation	Diagnosis and comparison group (*N*, age, IQ)*	Matching*	EEG or fMRI	Stimuli and task	Findings (RT = Reaction time)
			Fragile X syndrome		
Watson et al. (2008)	FXS: *N* = 13. Age: M = 15.5, SD = 2.4. IQ: WISC III: M = 61, SD = 14.8. DD (developmental delay) group: *N* = 13. M = 16.1; SD = 3.3. IQ M = 62.4, SD = 9.4. TD: *N* = 13. Age: M = 15.0, SD = 2.5. IQ: M = 116.8, SD = 11.6.	CA matched to TD, IQ and CA matched to DD	fMRI	Color photos of faces with neutral expressions that were (1) forward facing with a direct gaze, (2) forward facing with averted gaze, (3) averted face with direct gaze, and (4) averted face with averted gaze. Button press for averted or direct gaze.	Aberrant neural processing during gaze perception and a lack of neural adaptation to successive gaze stimuli were found in the group with FXS. Functional brain correlates related to a decreased ability to adapt to direct eye gaze stimuli. Behavioral data: Task accuracy differed between the TD group and other groups (but not between the DD and FXS groups). FMRI Data: Within-group comparisons of the contrast DirectGz-AvertedGz revealed significant activation in distinct regions: (1) FXS group showed significant activation in the left anterior insula. (2) TD group in the right parahippocampal gyrus and the left medial frontal gyrus. (3) DD group in the right midfrontal and parahippocampal gyri. Whole-brain ANOVA for the DirectGz vs. AvertedGz contrast revealed a main effect of group in the right cingulate gyrus, right midfrontal gyrus, and left insula. ROI analyses: main effects of group in the left amygdala and in the right STG. FXS had significant sensitization in the left amygdala which correlated negatively with performance on successive trials in the FXS group.
Garrett et al. (2004)	FXS: *N* = 15 but 4 discarded; all female. Age: M = 16.4, SD = 4.09, Range= 10–22; IQ: (WISC III for children, WAIS II for adults); M = 93.7, SD = 10.4. TD: *N* = 15 all female. Age: M = 15.5, SD = 3.4, Range = 10–22. IQ: M = 107.0, SD = 11.2). TD group had higher full-scale IQ score than FXS.	IQ matched and gender	fMRI	Color photographs of faces in four categories: (1) face forward with direct gaze, (2) face forward with averted gaze, (3) face angled with direct gaze, (4) face angled with averted gaze. Task 1: Subjects pressed a button if the face in the photograph was looking at them or another button if the person was looking away from them. Task 2: Subjects were required to indicate direction of gaze for faces and to alternate pressing the first and second button in response to the scrambled pictures.	Results included 11 subjects in the FXS group and 11 subjects in the TD. (1) Task Accuracy: TD had greater accuracy (2) Full scale IQ: Scores were correlated with task accuracy for both groups combined but not within each of the groups. Subsequent between-group analyses were covaried for IQ, which also controlled for between-group differences in the task accuracy. (3) RT: No group differences. (4) Brain activation (direct-averted faces): No differences comparing forward faces with angled faces. Brain activation (direct-averted gaze)—Three clusters of greater activation were noted in the TD group including STS, lingual gyrus and cerebellum. Two clusters of greater activation were noted in FXS relative to TD group including the right insula and the cerebellum. Activation FG did not differ between FXS and TD. Interaction between group and hemisphere showed TD right > left FG activation to all stimuli.

Hall et al. (2009)	FXS: *N* = 10, females; Age: (M = 18.7 years, SD = 3.81 years). IQ (test not specified) M = 86.3, SD = 16.41). TD: *N* = 10, female; Age (M = 14.7 years, SD = 2.95 years). IQ (M = 110.2, SD = 10.84)	MA matched.	fMRI	Two tones (standard and comparison); determine by button press whether the comparison tone was longer or shorter than the standard tone. In control task the stimuli were of equal duration.	Accuracy and RT did not differ between the groups. Brain Activation: FXS activation was more diffuse and distributed over a large number of regions. No greater activation in TD compared with FXS. IQ and age—no correlation with activated brain regions; in FXS only the left pons showed a significant (positive) correlation with mental age. Percent correct correlated with activation in the cerebellum in the TD group, and performance was significantly correlated with activation in middle temporal gyrus in the FXS group. In the FXS group, no significant correlation with FMRP level.
Hagan et al. (2008)	FXS: *N* = 10, female. Age: M = 16.4, SD = 4.9, range = 9.7–24.0 years. IQ: (WISC-III for children, WAIS III for adults) M = 91, SD = 16.2, range 75–124; TD: *N* = 10, female. Age: M = 15.6, SD = 4.2, Range = 8.4–22.9; IQ: M = 106.1, SD = 15.7, range 79–128. No age differences; trend for FSIQ differences between groups.	CA matched.	fMRI	Color photographs: happy, sad, neutral and scrambled faces. Press the left button if the person in the photograph appeared happy, a middle button if the person appeared sad, and a right button if a neutral or scrambled face appeared.	Accuracy: FXS participants were less accurate at recognizing neutral and scrambled faces relative to TD. No differences in the identification of happy or sad faces. RT: no differences. No correlation for either group between RT and FSIQ. Brain activation: increased left hemisphere activation in left medial frontal gyrus and left superior and middle temporal gyrus, left cerebellum and left pons among participants with FXS relative to TD. Overall more activation in FXS than TD.
Hoeft et al. (2007)	FXS: *N* = 10, all male. Age: M = 15.4, SD = 2.7; IQ (WISC-III for children, WAIS III for adult): M = 59.2, SD = 9.8). Idiopathic (DD)- *N* = 10, male. Age: M = 14.6, SD = 2.7; IQ: M = 65.3, SD = 13.8. TD: *N* = 10, male. Age: M = 16.7, SD = 4.2; IQ: M = 125.6, SD = 11.5. The three groups were matched for age and race/ethnicity. IQ of TD > DD = FXS	FXS and DD matched on IQ; FXS, DD, TD were matched for age and race/ethnicity.	fMRI	Visual go/no-go task: Press the button to every letter except X which occurred 50% of the time; Control task—press a button to every letter but no x's were presented.	No RT differences. Accuracy: DD sig lower go% correct, and a lower no-go% correct and overall task performance than TD and FXS (post hoc). No accuracy difference between TD and FXS. Brain Activation- task performance in FXS was associated with left VLPFC, and not by right fronto-striatal region activation. Interactions between FMRP and right striatal dysfunction are associated with this putative compensatory left VLPFC activation in FXS. The extent of right fronto-striatal dysfunction in FXS is correlated with FMRP levels.
Tamm et al. (2002)	FXS: *N* = 14, female. IQ WISC-III or WAIS: M = 84.43, SD = 15.79; TD: *N* = 14, female IQ: M = 117.93, SD = 13.21; Child Behavior Checklist (CBCL) scores: TD had lower attention and thought problem subscale score. Participants ranged in age from 10–22 (M = 15.43, SD = 3.79). IQ higher in TD.	CA matched while IQ was controlled.	fMRI	Two kinds of Stimuli conditions: Neutral condition: the word *fish* was presented 1, 2, 3, or 4 times on the screen (15 trials). Interference condition: Subjects were presented the words *one*, *two*, *three*, and *four*, presented one, two, three, or four times on the screen (15 trials). TASK (Stroop): Press a button that corresponded to the number of words on the screen.	Behavioral results: FXS more affected by the interference condition (slower RT). Evidence that individuals with FXS sacrificed speed for accuracy, while the controls did not. Brain activation: Both groups recruited the prefrontal cortex (middle and inferior gyri) during the interference condition, for FXS this activation was bilateral, while controls' activation was primarily in the left hemisphere. Between-group comparisons indicated that FXS did not show greater activation than controls in any brain area.

(*continued*)

TABLE 1.1 (*Continued*)

Citation	Diagnosis and comparison group (*N*, age, IQ)*	Matching*	EEG or fMRI	Stimuli and task	Findings (RT = Reaction time)
Van der Molen et al. (2012)	FXS: *N* = 16 males, Age: M = 29.6, Range= 18–42 years; Raven Standard Progressive Matrices RAW SCORES: M = 19.88, SD = 8.15, Raven IQ was equivalent to an average mental age of 7.73 years (SD = 1.59). TD: *N* = 20 males, Age: M = 29.2, Range = 19–47; Raven Standard Progressive Matrices M = 55.65, SD = 3.76; Raven Standard Progressive Matrices Raw scores were sig. lower in FXS than TDs.	CA matched.	EEG	75 ms 1000 Hz and 1500 Hz sinusoidal tones with 5 ms rise and fall time, presented through headphones, at 80 dB SPL. The interstimulus interval was 1,000 ms. To counterbalance which tone was deviant/standard for each participant, half of the participants were presented with the 1000 Hz tone as standard and the 1500 Hz tone was deviant (and vice versa for the other half). Task: All participants watched a silent movie and were told that the auditory stimuli were irrelevant.	N1: amplitudes to standard tones were larger in FXS males than in controls but larger for deviant tones than standards for the comparison participants. N1 Habituation): In controls, amplitude of the N1 elicited by late standards was significantly smaller than the amplitude elicited by early standards (mean difference = −1.20 P2: amplitudes were significantly larger in FXS than in control group to both standard and deviant stimuli). P2 amplitudes were largest at Cz and smallest at Fz in controls and largest at Cz and Oz in FXS males.
Van der Molen et al. (2012)	FXS: *N* = 16 males, Age: M = 29.6, Range = 18–42 years, Raven Standard Progressive Matrices RAW SCORES: M = 19.9, SD = 8.2. IQ couldn't be calculated but performance was equivalent to an average mental age of 7.7 years (SD = 1.6), PPVT 3rd edition (average verbal mental age of 9.1 years, SD = 2.7. TD: *N* = 22 males. Age: M = 29.2, Range = 19–47, Raven Standard Progressive Matrices: M = 55.65, SD = 3.8; Raven IQ: M = 121.5, SD = 25.8). Raven Standard Progressive Matrices Raw scores were sig lower in FXS than TD.	CA matched.	EEG	Acoustic stimuli: 1000 Hz and 1500 Hz sinusoidal tones with a duration of 100 ms, including 5 ms rise and fall times. Visual stimuli: blue and yellow colored smiley faces that were viewed from 70 cm distance and presented on a black background in the center of a 17-inch laptop. TASK: A target (deviant) or a nontarget stimulus (standard) was presented for 100 ms (similar in both auditory and visual tasks). Participants were required to respond to the target stimulus (blue or yellow smiley face; 1,000 Hz or 1,500 Hz tone). Responses were registered within the 100–1200 ms response window after stimulus onset. Yellow smiley faces and 1000 Hz tones were used as target stimuli. Participants were instructed to responded as quickly and accurately as possible to the onset of a deviant stimulus by pressing a button on the computer.	Behavioral data: FXS males showed more false alarms, and were slower on both the visual and auditory tasks than controls. FXS males committed significantly more false alarms on the auditory than on the visual task suggesting that selective attention is more compromised in the auditory than in the visual modality in FXS. N1 auditory: N1 amplitude was larger for both stimuli in FXS males compared with controls; no group differences in P2 auditory amplitude were noted. N1 visual: peak amplitudes were maximal at Oz in control participants and at FCz in FXS males. N1 amplitudes were significantly larger in FXS males than in controls for both stimuli, but only at FCz. No differences in Visual P2 were noted between groups. Visual P3b: P3b component was larger in controls than in FXS males, in both auditory and visual modalities. For FXS males, the P3b component was significantly larger in the visual modality as compared with the auditory modality.
Castren et al. (2003)	FXS: *N* = 4 boys. Age: M = 11.6, SD = 2.8, Range = 7–13; and one 21 years old. TD- *N* = 4 boys, Age: M = 10.6, SD = 0.6	CA matched.	EEG	(1) Random stimulus sequence of tones consisting of 85% standard (800 Hz) and 15% of deviant (560 Hz) tones. (2) Trains of four identical standard tones. The recordings were performed while the children were watching a silent cartoon on a TV screen, and they did not attend to the tones.	(1) N1 amplitude is larger in children with FXS than in controls. (2) The first half of N2 component for controls is significantly more negative than that of FXS. (3) A significant difference between groups was present in the global-field-power waveforms implying differences in the total brain activity. (4) The topographic distribution of the N1: the N1 peak in children with FXS was well defined when compared with that of controls, maximum amplitude was located frontocentrally. The N1 scalp distribution in FXS patients was similar to controls, whereas the N2 in FXS was located more centrally than controls.

			Down syndrome		
Wetter et al. (1999)	DS: *N* = 20 Adults, Age: M = 26.0, SD = 10.0; IQ: M = 52.5, SD = 7.1; Dementia was assessed using the Dementia Rating Scale-DRS: M = 99.1, SD = 17.9. TD= *N* = 20, Age: M = 25.7, SD = 10.3. IQ was not administered to TD group	CA matched; Within group DS assessing relationship between olfactory ERP and dementia.	EEG	Olfactory stimuli (banana odor) were presented via an olfactometer. 2-alternative (odorant and blank), forced choice, ascending method of limits (increased concentration of banana odor) ERP measured at the Fz, Cz, Pz sites for 2000 ms (500 ms prestimulus and 1,500 ms post).	OERP components: the amplitudes and latencies of the OERP components N1, P2, N2, P3, and the interpeak amplitudes N1-N2, N1-P3 were analyzed. Latency: DS demonstrated delays in initial sensory processing. DS demonstrated longer latencies at all components compared with TD. In addition, N2 latency showed a significant effect of age ($F(1,37) = 6.64$, $P < 0.005$), with latencies increasing from adolescence to adulthood. OERP amplitude—not sig. Odor Threshold: DS group had higher thresholds (poorer sensitivity) than TD. Negative correlation between smell threshold and the latency of early OERP components (N1, P2 and N2). Dementia rating scale—negative correlation between DRS scores and P3 latency at all electrodes.
Yoder et al. (2006)	DS: *N* = 10 children (6 males). Age: M = 5.9, SD = 1.4, range 4.33–8.25 years. Nonverbal MA- Leiter-R age equivalency M = 3.5, SD = .8, Nonverbal IQ: M = 66.7, SD = 8.7, Grammatical morphology comprehension: M = 3.7, SD = 1.9; Percentile ranking on Grammatical Morphology subscale of the Test of Auditory Comprehension of Language-TACL-3 (M = 5%, SD = 4.6%) indicated that the sample was quite impaired as a whole (M = 5%, SD = 4.6%), with all but 1 participant falling below the 10th percentile. No control group.	DS split into two subgroups based on their performance on the TACL-3. Then DS was compared based on age, IQ and MA.	EEG	A passive task with three contrasts of consonant-vowel syllables were selected: (1) ga vs. da; (2) ga vs. ba; (3) da vs. na.	ERP difference waves to two consonant-vowel syllables were strongly associated with the degree of impairment in morphological comprehension. Results demonstrated a greater differentiation between event-related potential waves for the less impaired subgroup than the more impaired subgroup within the targeted latency range indicated by the temporal principal components analysis factor of interest. Age, IQ, and MA were nonsignificantly correlated with TACL-3.
Lalo et al. (2005)	DS: *N* = 20 Adults (10 males). Age: 18–31, M = 24.10 years, SD = 49 months. TD: *N* = 20 adults (10 males), Age 19–31; M = 25 years, SD = 44 months.	CA matched.	EEG	3 conditions: passive, simple—required to press a button on the armrest chair when detecting target tones and complex—required to aim with their dominant hand from the armrest at a target fixed on their chest when detecting target tones; presented as oddball.	(1) Passive condition: N1 and P2 components were reliably present in all participants. TD: infrequent stimuli usually triggered a MMN under the passive condition. In addition, a P3a component was elicited in about half of the participants, while a P3b was observed in 70%. In comparison, these three components were observed in only 10–25% and their latency tended to be longer in the DS group. (2) Active condition: TD- components N2b and P3b were usually seen under the active conditions, whereas in the DS group the N2b was often missing or delayed. The P3b was present in most participants with DS (55–65% compared with 75–85% in the TD group), albeit with a latency longer than the TD. RT = was shorter in TD than in DS. In addition, RT was significantly longer under the simple > active condition for the DS group only.

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TABLE 1.1 (*Continued*)

Citation	Diagnosis and comparison group (*N*, age, IQ)*	Matching*	EEG or fMRI	Stimuli and task	Findings (RT = Reaction time)
Jacola et al. (2011)	DS: *N* = 8, 5 female. Age: 18, SD = 3, Range =12–26. IQ: Stanford-Binet Intelligence Scale, 5th Edition (SB-V). Full scale IQ: M = 44, range = 40–50. Peabody Picture Vocabulary Test (PPVT-III): M = 57, range =40–83. TD: *N* = 12, 5 female. Age: M = 19, range = 12–26 years. SB-V full scale IQ, M = 106, range 88–124. PPVT-III: M = 107, range = 95–133.	CA matched.	fMRI	Experimental condition: press a button for pictures of farm animals. Control condition: Scrambled animal images were presented and participants pressed a button for each image.	Qualitatively and quantitatively different pattern of activation for DS in comparison age-matched TD. Increased activation in DS bilaterally for middle frontal gyrus and regions of the left parietal lobe. An overall reduction in spatial extent of neural activation and atypical patterns of activation were found in individuals with DS.
			Williams Syndrome		
Haas et al. (2009)	fMRI Study: *N* = 27, 13 TD, 5 males; 14 WS, 7 males. EEG Study: *n* = 70, 25 TD, 11males; 30 WS, 11males; 15 with developmental delay, 8 males. Both fMRI and EEG: 11 WS participated in both, 4 males. Age: M = 31.13, (SD = 7.55). Williams Syndrome: *N* = 33, 13 males. Age, M = 31.01 (SD = 8.80). Comparison Group 1(TD): *N* = 38, 18 males. Age, M = 29.71, SD = 9.52. IQ: M = 106 (SD = 11.8). Comparison Group 2 (idiopathic ID but not autism): *N* = 15, 8 male. Age: M = 28.07, SD =8.8; IQ: M = 62, SD = 8.8). WS and DD were matched on full-scale IQ (WS: M = 65, SD = 6.8, DD: M = 62, SD = 8.8).	CA matched to TD, IQ matched for DD. No significant between groups' ages or proportion of females to males.	Two separate studies, 1 fMRI and one EEG.	Color images of males and females with: happy, fearful, or neutral expressions. Participants identified if each face was male, female, or scrambled by button press.	Behavioral findings: Williams syndrome slower and less accurate compared with age-matched participants but equal to MA matched participants. fMRI and EEG findings: participants with Williams syndrome exhibited heightened amygdala and cortical responses to happy/neutral. WS—exhibited greater right amygdala in happy condition compared with neutral condition. TD—did not exhibit greater left or right amygdala activation to happy condition compared with neutral condition than the WS group. WS exhibited significantly greater right amygdala reactivity to happy compared with neutral. TD: No significant left or right amygdala activation in response to happy compared with neutral was observed. Fearful/neutral group differences: TD exhibited greater right amygdala activation than WS. TD exhibited greater right amygdala reactivity to fearful compared with scrambled faces (nonsocial) at the corrected statistical threshold. There was no significant difference in amygdala reactivity to neutral relative to scrambled faces between the WS and TD groups. *Amygdala with IQ, RT and accuracy:* (1) IQ as a covariate with BOLD signal extracted from the right amygdala yielded no significant correlations between IQ and amygdala activity either in response to happy ($p = 0.57$) or fearful ($p = 0.48$) facial expressions within the WS group. (2) RT and accuracy as covariates with BOLD signal extracted from the right amygdala yielded no significant correlations

					between either RT or accuracy and activity either in response to happy or fearful facial expressions within the WS group. ERP happy condition: P300–500-condition × group interaction indicated that the P300–500 response to happy versus neutral facial expressions was significantly different between the three groups. Happy minus neutral facial expressions was larger for the WS than for the TD group and the DD group (but did not differ between the TD and DD groups). ERP fearful condition: P500–700-condition × group interaction indicated that the N200 to fearful versus neutral facial expressions was significantly different between groups in mean amplitude. No condition × group effects for peak latency. Between-group comparisons showed that the N200 difference wave to fearful minus neutral facial expressions tended to be greater (more negative) for the WS than for the TD group over the left hemisphere and was greater (more negative) for WS than for the DD group. In contrast, the effect was smaller (more positive) for the DD than for the TD group. TD group: The N200 did not differ in mean amplitude to fearful versus neutral expressions or peak latency. DD showed increased N200 amplitudes to fearful relative to neutral faces.
Hass et al. (2010)	WS: $N = 12$ Adults (8 Female, 4 Male) Age: M = 29.46, SD = 8.07, Range = 18.03–43.58	No comparison group.	fMRI	Colored pictures of headshots of young adults displaying fearful, happy or neutral expressions and scrambled images. Stimuli presented using an event-related design with the four experimental conditions and a resting baseline. Subjects were instructed to judge if each face was either male or female or scrambled by responding with their index finger.	(1) Behavioral data: Mean RT: 981.46 ms and accuracy rates- 72.16%. No condition differences (fearful, happy, neutral and scrambled) in RT($F = .47$, $P = .70$) or accuracy ($F = .08$, $P = .97$). In addition, no relations between either RT or accuracy and the sociability measures were found. (2) Indiscriminate sociability and amygdala response to facial expression: Social approach scores were regressed against amygdala response to facial (fearful, happy and neutral combined) expressions compared with scrambled images. No significant positive or negative relationships between social approach scores and either left (group averaged ROI: R2 = .33, $p = .40$; standardized ROI: R2 = .27, $p = .30$) or right (group averaged ROI: R2 = .11, $p = .70$; standardized ROI: R2 = .04, $p = .61$) amygdala response to facial expressions compared with scrambled images, even when age, sex, and handedness were entered as covariates. Furthermore, no significant relationships were observed between social approach scores and either hippocampus and parahippocampal gyrus response to facial expressions.

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TABLE 1.1 (*Continued*)

Citation	Diagnosis and comparison group (*N*, age, IQ)*	Matching*	EEG or fMRI	Stimuli and task	Findings (RT = Reaction time)
Thornton-Wells et al. (2011)	WS: *N* = 10, 6 females. Age: M = 21.8, SD = 1.0 IQ: Kaufmann Brief Intelligence Test-2: M = 79.20, SD = 17.84; 2 control groups of TD: selected cutoff scores (inhibited (IT) ≥ 2.6, uninhibited (UT) ≤ 1.9) Temperament (IT)-*N* = 10, 6 females. Age: M = 24.3, SD = 1.93 IQ: Kaufmann Brief Intelligence Test-2: M = 117.30, SD = 13.49. 2-Uninhibited Temperament (UT)-*N* = 10, 6 females. Age: M = 24.5, SD = 1.98; IQ: M = 108.33, SD = 9.03.	TD from each temperament group, based on the traits of IT and UT were matched on gender to WS group.	fMRI	Social and nonsocial images across three emotions (happy, fear and neutral) in a passive viewing task.	WS-IT: Fear nonsocial images: WS > IT controls in left amygdala relative to the IT control group even in relation to neutral expressions. No differences for other comparisons WS (neutral and happy nonsocial images). WS-UT: when viewing social images (faces). Larger left amygdala responses in WS group for neutral social images, compared with the UT control group. When comparing the happy faces to the neutral faces, the UT group had significantly greater left amygdala response than the WS group.
Golarai et al. (2010)	WS: *N* = 13, Age: M = 29.9, SD = 2.6,TD: *N* = 13, Age: M = 30.0, SD = 2.3. IQ (WAIS-R or WAIS-III) WS: performance IQ: M = 71.08, SD = 2.3, Verbal IQ: M = 64.92, SD = 2.5: FSIQ: M = 66.3, SD = 2.6. TD: performance IQ: M = 117.9, SD = 3.5, Verbal IQ: M = 115.6, SD = 4.6; FSIQ: M = 119.0, SD = 4.2. Benton recognition test on upright face: WS: *N* = 13; M = 20.8, SD = 0.7. TD: *N* = 9 of 13; M = 22.63, SD = 1.05.	CA matched and matched Benton face recognition scores.	fMRI	Passive viewing of grayscale images of faces (male, female, various ages, races, expressions and views), objects (abstract sculptures), places (indoor and outdoor), textures (created by randomly scrambling object pictures into 225, 8 x 8, pixel squares).	(1) Average rFFA (right Fusiform Gyrus) volume was two times larger and left FFA volume was 2.5 times larger among WS than TD. The proportional volume of the FFA relative to the anatomical volume of the FUS (fusiform) gray matter was also significantly higher in WS than in TD even when matched on total volume. (2) Variation in the absolute volume of the FFA within each group did not correlate with the anatomical volume of the FFA, gray matter content, or subjects IQ or age.
Mimura et al. (2010)	WS: *N* = 7, all females. Age: M = 34.0, SD = 12.17, All were ELN negative on chromosome 15 by FISH. All exhibited the medical or clinical features of the WS phenotype including cognitive, behavioral, and physical profiles. IQ Wechsler Adult Intelligence Scale third edition (FSIQ: M = 68, SD = 8.7; VIQ: M = 74, SD = 8.7; PIQ: M = 65, SD = 8.8). TD: *N* = 7, all females. Ages (M = 35.7, SD = 11.1). IQ: FSIQ: M = 115SD = 12.0; VIQ: M = 112, SD = 14.5; PIQ: M = 114, SD = 8.2.	CA matched.	fMRI	(1) Match Affect Paradigm (MAP): consisted of 90 achromatic face stimuli presented in an event-related FMRI paradigm: Two faces were presented that were either congruent for negative or positive affect or incongruent. Participants determined whether the faces matched or not. (2) Control task: Subjects matched gender (male, female) of neutral faces rather than emotions.	(1) Behavioral performance: No difference in accuracy between WS and TD when controlling for FSIQ. (2) Brain Imaging: (a) WS < TD for negative compared with positive valance face stimuli in both right amygdala and right lateral OFC but WS > TD for right medial OFC for negative compared with positive emotional face stimuli. (b) Medial OFC, WS to TD showed significantly reduced activation to negative face stimuli relative to positive stimuli and greater activation to negative stimuli. (c) No correlations between IQ and whole brain activation for either group; significant positive correlation between right lateral OFC activation and IQ for the positive vs. negative valance contrast in the WS group. (d) Control gender matching task showed nonsignificant effects in all these regions and analysis.

Mobbs et al. (2007)	WS: *N* = 10, 8 females. Ages: M = 31.10, SD = 9.7, Range = 15.5–48.4), IQ: VIQ: M = 71.6, SD = 7.6; PIQ: M = 65.6, SD = 8.1; FSIQ: M = 67.3, SD = 7.5. TD: *N* = 8, 7 females. Ages: M = 35.2, SD = 10.10, Range = 24.0–54.7. IQ: VIQ: M = 113.5, SD = 14.7; PIQ: M = 111.2, SD = 8.1; FSIQ: M = 114.2, SD = 9.8	CA matched.	fMRI	A nonverbal global processing task was used: (1) 72 experimental stimuli were either a large concentric triangle or square consisting of smaller triangles or squares; (2) 72 control stimuli consisted of a large, single-lined triangle or square of the same dimensions.	There were significant IQ differences between the groups. WS were less accurate but not slower than TD. No correlation between IQ and global task RT or accuracy. FMRI: between group analysis—greater activation in WS than TD in right MFd. significantly increased activation in WS was seen in hippocampus and parahippocampal gyrus, right lateral geniculate, insula, thalamus, superior temporal gyrus, middle temporal gyrus, orbital frontal cortex, middle frontal gyrus and medial aspects of the precuneus. No significant correlation was found between activation and either IQ or performance accuracy in WS.
Key and Dykens (2011)	WS: *N* = 21, 12 males. Age: M = 26.24, SD = 8.26. IQ: Kaufmann Brief Intelligence Test-2 = M = 74.25, SD = 17.19; TD: *N* = 16, 7 males. Age: M = 29.64, SD = 11.77. IQ scores for TD participants assumed to be in the normal range but not tested.	CA matched.	EEG	Oddball paradigm with letter stimuli that could appear as a global form (big letter) or a local element (small letter) but never in same trial. Participants responded yes/no regarding the presence of a target (H) that could occur at either the global (20% probability) or the local level (20% probability).	RT: TD showed global targets associated with shorter RT than standard stimuli or local targets and no RT differences between local targets and standard stimuli. However, WS RT data failed to identify any differences among the conditions. Accuracy rates for TD across all three conditions were near perfect. WS detected global targets more accurately than local targets. ERP: TD: trend for reduced P1 amplitude P1 amplitude for global targets compared with standard stimuli). WS: relative to the standard stimuli, global targets elicited a smaller P1 peak with shorter latency. TD condition differences were present for the centro-parietal P3b amplitude while WS showed no significant effects for the centro-parietal P3b amplitude.
Levitin et al. (2003)	WS: *N* = 5, 2 males. Age: M = 28.8, SD = 14.6; IQ = M = 63.0, SD = 17.2. TD: no information provided	Age, handedness, gender, and musical experience matched depending on what they measured.	fMRI	Passive listening of noise, music, and silence.	TD: consistent bilateral activation in the superior temporal gyrus and middle temporal gyrus which were not present in WS. WS activations were more widespread and diffuse, recruiting regions in the amygdala and cerebellum. Both groups displayed bilateral temporal lobe activation for music compared with noise and rest. However, these activations were decreased for WS than TD.
Paul et al. (2009)	WS: *N* = 17, 10 females. Age: M =30.6 years. IQ: Wechsler: Full Scale IQ M = 67.5, SD = 11.3 range 47–82. Verbal IQ M = 72.8, SD = 7.8, range 59–89. Performance IQ: M =64.4, SD = 10.3, range 44–83. Peabody Picture Vocabulary Test age equivalents: M = 12.6, SD = 4.5, range 5.8–22. Visuomotor Integration (VMI) Nonverbal: Figure Drawing Age Equivalent: M = 5.69, SD = 1.6, range 4.1–11.3. TD (CA matched group): *N* = 17. Age: M = 31.0, SD = 11.2. TD: MA-matched: *N* = 17, 9 females. Age: M = 8.8, SD = 0.7.	CA and MA (two different comparison groups).	fMRI	Visual matching of facial identity of black and white photographs appearing in one to 12 possible positions. Two faces sequentially, followed by a delay 500 or 1750 ms delay. A 3rd face appeared and participants indicated whether the test stimulus matched either of the two reference stimuli by hitting the yes or no button.	Behavioral Findings: WS slower and less accurate that CA but not MA comparison participants. Functional neuroimaging: FMRI responses were generally similar in WS participants and MA controls with both groups displaying less robust activations than CA controls. Amygdala response in WS participants showed no activation in contrast to both CA and MA comparison participants.

the other half involved ERPs or MEGs to assess basic auditory processing. Although there is very little overlap with respect to tasks across studies, both the Stroop task and the go/no-go tasks can be considered measures of executive function (specifically inhibition), while the emotion identification task in females and the eye-gaze direction detection task in males with fragile X can be considered as assessing the social-cognitive correlates of the disorder. The auditory ERP studies allow researchers to assess the integrity of the auditory pathway as well as the ability of individuals with fragile X to habituate to sounds and respond to auditory novelty. These three areas are all considered to be fundamentally impaired in the phenotypes of both males and females with fragile X syndrome (e.g., Hagerman, 1996; Turkstra, Abbeduto, Meulenbroek, 2014).

Auditory Processing Assessed by ERP and fMRI Individuals with fragile X demonstrate sensory difficulties, and specifically auditory hypersensitivity, as measured by parent report. These behavioral findings have been partially substantiated by both MEG (Rojas, Benkers, Rogers, Teale, Reite, & Hagerman, 2001) and ERP studies (for a recent review of electrophysiological findings among individuals with fragile X syndrome in which developmental level is considered in the interpretation of findings, see Knoth & Lippé, 2012). Findings are consistent for certain ERP components which include an overall increased amplitude of the N100, an automatic component elicited by the onset of a sound (Castren, Paakkonen, Tarkka, Ryynanen, & Partanen, 2003; St Clair, Blackwood, Oliver, & Dickens, 1987; Rojas et al., 2001; Van der Molen, Van der Molen, Ridderinkhof, Hamel, Curfs, & Ramakers, 2012, 2012), albeit with findings of decreased habituation of the N100 (Castren et al., 2003; Van der Molen et al., 2012) in relation to chronologically age-matched participants. In addition, a consistent attenuation of the P300, which indexes attention and/or orientation to novelty, has been noted in relation to typically developing CA-matched comparison participants (St Clair et al., 1987; Van der Molen et al., 2012, 2012) but not in relation to MA-matched individuals with Down syndrome (St Clair et al., 1987), indicating that the physiological responses of individuals with fragile X are of similar amplitude to those of individuals of a similar MA. These findings suggest that individuals with fragile X overrespond to sound, and do not habituate (decrease in response to the repeated presentation of a sound) to auditory stimuli in the same manner as typically developing individuals, although the P300 findings of differences relative to CA- but not MA-matched participants highlight that matching strategies need to be considered in all interpretations and conclusions.

In addition to findings of consistent atypicality in early physiological responses to auditory stimulation, inconsistent findings are noted for other ERP components, including the P2, a physiological response that is greater for infrequent simple targets than frequent targets or frequent distractors, and the N2, which is greater for attended versus unattended stimuli and can index the detection of novelty, stimulus identification, or shifts in attention. St Clair et al. (1987) found increases in P2 but no difference in N2 in relation to typically developing comparison participants using a passive oddball task in which the participants watched a silent movie while two different sounds (one, the frequent, occurring on 80% of the trials and the other, the oddball, occurring on 20% of the trials) were played in the background. In contrast, Van der Molen et al. (2012) found an increased P2 and an increased N2 using a similar passive task. In a subsequent study, Van der Molen et al. (2012) required participants to actively detect oddball targets, and found no P2 differences but an increased N2 in relation to CA-matched typically developing comparison participants. These findings suggest that processing differences depend on whether participants are actively engaged in an experiment or passively listening, which may or may not be related to MA. The implications of these studies are diminished by small groups and the use of CA matching (with the exception of St Clair et al., 1987, who compared individuals with fragile X to both CA-matched typically developing peers as well as MA-matched peers with Down syndrome).

In the only MEG study conducted with participants with fragile X, the participants watched a silent movie while pure tones were played, thereby allowing for the assessment of basic auditory processing (Rojas et al., 2001). (Briefly, MEG is a technique that combines some of the temporal resolution of ERPs with the some of the spatial resolution of fMRI.) Rojas et al. compared 11 participants with fragile X (six female, five male) to typically developing peers matched on CA and reported an increased amplitude of the mN100 component, the MEG analogue of the auditory N1 in EEG studies, among the participants with fragile X, suggesting greater neuronal activation in response to sounds. However, these findings need to be qualified due to the differences in developmental level between the groups, as the IQs of the typically developing comparison participants were more than double that of the participants with fragile X, and well above the average range. Given these vast differences in IQ between the groups and the notion that CA affects the amplitude of ERP responses (Gomes et al., 2001), we need

to consider whether the amplitude differences between the groups might reflect meaningful phenotypic differences or are a confound arising from the significant differences in developmental level of functioning (i.e., MA) between the groups. Also given the IQ differences between males and females with fragile X, whose ERPs were averaged together into one group, gender differences may have confounded the findings. If MA affects the magnitude of ERPs, then averaging females with high MA (and their characteristic ERPs) with males with low MA (and their characteristic ERPs) may have led to an average ERP response that is characteristic of neither the males nor the females in the sample. Accordingly, the group-level analyses comparing typically developing and fragile X groups may not reflect any meaningful differences.

In spite of these major caveats, other evidence has also supported the notion that auditory processing in fragile X is atypical. For example, Castrèn, Paakkonen, Tarkka, Ryynanen, and Partanen (2003) found higher N100 amplitudes using a similar passive paradigm and ERPs among a small sample of children with fragile X compared with CA-matched typically developing children, providing further support for the notion that basic auditory processing appears to be atypical among individuals with fragile X. However, these findings must be considered in light of the difference in level of functioning between the participants with fragile X and the typically developing participants and very small group sizes. Nonetheless, ERP and MEG findings of basic auditory processing in fragile X are consistent with those of the FMR1 knockout mouse, an animal model of the disorder, which also suggest auditory hypersensitivity. In addition, the knockout mouse also shows deficits in cerebellar learning that are temporally sensitive, a key factor in auditory processing (Chen & Toth, 2001).

Based on these links between ERP findings of basic auditory differences and mouse models of fragile X, Hall, Walter, Sherman, Hoeft, and Reiss (2009) sought to assess the ability of females with fragile X and MA-matched typically developing female participants to make auditory temporal discriminations and measured the relationship between this ability and activations in sensory areas using fMRI. Although no differences in behavioral performance as measured by response time and accuracy were noted between the participant groups in their ability to assess whether a comparison tone was longer or shorter than a standard tone, fMRI activations differed between the groups.

The activation differences were compared by subtracting activations to the task condition described above with a control condition in which the participants were asked to respond to a button press after the presentation of two identical tones. Hall et al. (2009) noted that these two conditions were identical in every way, except that in the control condition the participants did not have to make temporal discriminations (the tones were always of equal duration, though participants were not told this). The primary finding was that subtracting activations between the discrimination and control tasks yielded more diffuse areas of activation in frontal, temporal and limbic regions for the participants with fragile X, whereas for the typically developing participants, the subtraction led to focal activations in parietal and occipital regions. This latter finding is somewhat surprising as Hall et al. were trying to isolate an auditory temporal discrimination but report activations in both the parietal lobe which is related to tactile processing, number knowledge, and multisensory integrations and in the occipital lobe which houses the visual regions, neither of which should have been involved in the task processing. Direct group comparisons yielded increased left hemisphere activations for the participants with fragile X in the frontal (left medial frontal gyrus) and temporal (left superior and middle temporal gyrus, left cerebellum and left pons) regions. No areas of the brain were more active among the typically developing than among the participants with fragile X, suggesting that the participants with fragile X used more processing resources than the typically developing participants. Hall et al. examined the associations among IQ, age, and activation levels and noted that their findings could not be attributed to these potentially confounding variables because the correlations among age, IQ, and activated cortical and subcortical regions were not significant.

Hall et al. (2009) also found that task performance correlated with cerebellar activations in the typically developing group but with middle temporal gyrus for the fragile X women, and that contrast values of the significantly activated brain regions did not correlate with levels of FMRP among the females with fragile X. These findings suggest differences in activation patterns on this simple task despite similar behavioral performance, and that these differences were related neither to IQ, age, nor the severity of fragile X, as genetically defined. However, the lack of significant correlations could also be due to a restricted range in these variables, the small sample size, or the lack of correction for multiple comparisons in their fMRI results, a problem which plagues fMRI research and which some authors suggest will always lead to increases in false positive discovery rates and subsequent difficulties in interpreting findings (see Bennett, Wolford, & Miller, 2009; Poldrack, 2012).

Overall, simple temporal discrimination abilities among females with fragile X syndrome appear commensurate with MA, although task performance seems supported by different brain regions, which could reflect either increased mental effort or some sort of compensatory processing.

Gaze Processing as Assessed by fMRI Garrett, Menon, MacKenzie and Reiss (2004) and Watson, Hoeft, Garrett, Hall and Reiss (2008) conducted similar studies of gaze processing among females and males with fragile X, respectively. Gaze avoidance is a hallmark symptom of fragile X even in the absence of a comorbid diagnosis of ASD, and generally occurs across both males and females with the disorder. Both studies involved similar stimuli, task, and methods in which participants were presented with pictures of faces (angled or forward facing) whose gaze was either direct or averted. The participants responded by button press as to whether the face was looking at them or away from them. Garrett et al. compared females with fragile X with IQs in the average range to typically developing females matched on age. However, despite the attempt to include only females with fragile X with average IQs, the IQs of the typically developing comparison participants were significantly higher than those of the fragile X participants. In a different approach, Watson et al. compared boys with fragile X to both typically developing children of the same CA and individuals with a developmental delay (DD; group composition not mentioned but specified as not autistic) matched on the basis of both age and IQ. With respect to task performance (RT and accuracy), the typically developing groups in both studies performed better than the individuals with fragile X. The boys did not differ in performance from the IQ matched group of DD participants, but the importance of this finding is negligible due to the problems in methodology and interpretation associated with the use of mixed etiological comparison groups. A significant correlation between IQ and task performance was noted for females, but not for males when compared with participants of equivalent MAs. That is, both males and females with fragile X appear to display a relationship between performance and developmental level. In neither study were RT differences found across the groups.

Group differences in the processing of direct versus averted gaze between individuals with fragile X and their respective comparison participants were noted in both the Garrett et al. (2004) and Watson et al. (2008) studies. Activations were similar between the participants with developmental delays and the typically developing participants, but activation patterns differed across studies with the exception of the superior temporal sulcus (STS), which showed greater activation in the typically developing groups as compared with the fragile X boys (Watson, 2008) and girls (Garrett, 2004). The finding of completely different activation patterns, even among the typically developing participants, is puzzling as essentially identical tasks yielded very different findings. The most we can conclude from these fMRI findings is that individuals with fragile X showed a relatively consistent decrease in activation in the STS, an area generally associated with the perception of other's gaze (Campbell, Heywood, Cowey, Regard, & Landis, 1990) and biological motion (Grossman & Blake, 2002).

Overall, the findings from the neuroscience studies of individuals with fragile X suggest both that auditory processing appears atypical in relation to CA-matched participants but not in relation to MA-matched participants (at least for the P300) and that gaze processing appears atypical in fragile X in relation to both CA- and MA-matched comparison participants. MA among persons with fragile X was, as expected, consistently linked to behavioral performance, but less so in relation to brain activations related to behavioral tasks.

Persons with Down Syndrome.

Simple Sensory Processing in Down Syndrome Using ERPs Many ERP studies of participants with Down syndrome have involved no-task paradigms in which participants just passively listen to sounds or view pictures while brain activity is recorded. This allows for the assessment of basic sensory function and is generally used to assess afferent (bottom-up) rather than efferent (top-down) pathways without requiring participants to complete an experimental task. The advantage of these studies is that they can be conducted in lower functioning individuals and are not tied to cognitive functioning. The disadvantage, of course, is that they are not informative about cognitive, or any other aspect of, functioning. Briefly, evidence from passive studies of auditory and visual functioning suggests that basic auditory processing of tones among individuals with Down syndrome is atypical, with reports of longer N1 latencies and higher P2 amplitudes in infants relative to CA-matched typically developing infants (Barnett & Lodge, 1967; Seidl, Hauser, Bernert, Marx, Freilinger, & Lubec, 1997), as well as an attenuated habituation to visual stimuli in frontal regions (but habituation was observed in other regions as well as behaviorally; Karrer, Karrer, Bloom Chaney, & Davis, 1998; Karrer, Wojtascek, & Davis, 1995). These findings appear to be consistent across childhood with findings of an attenutated P3 response during repeated auditory stimulation.

In addition to the studies involving responses to simple tones, Yoder, Camarata, Camarata, and Williams (2006) assessed the relationship between standardized measures of grammatical morphology and ERP responses to different consonant-vowel syllable pairs among individuals with Down syndrome. They divided a group of participants with Down syndrome into high and low grammatical morphology skill sub-groups (although the majority of participants fell below the 10th percentile) and found increased differentiation between syllables in the ERP waveforms among participants in the less-impaired group than among those who were more impaired, suggesting a relationship between grammatical abilities and brain responses. These findings suggest that increased mental effort is required for individuals with Down syndrome in the processing of basic sounds relative to their same-aged peers; that this finding is sustained over age, and that grammatical skills can reliably be differentiated among persons with Down syndrome using ERP technology. No studies of passive processing involved MA matching strategies and so, again, the meaningfulness of these findings are difficult to evaluate.

To assess whether the need to prepare a motor response influences the speed of perceptual auditory processing among individuals with Down syndrome, Lalo, Vercueil, Bougerol, Jouk, and Debu (2005) examined auditory processing and its relationship to movement complexity among adults with Down syndrome and CA-matched typically developing comparison participants. They used passive, simple active (button press responses) and complex active (motor movement to a spot on their chest) versions of an auditory oddball task. Lalo et al. noted RT differences between the groups as the responses under the simple task conditions were longer than the complex task condition among the participants with Down syndrome, but did not differ among the typically developing participants. Auditory N1 latencies were longer and auditory P2 responses were larger for the participants with Down syndrome than for the comparison participants when comparing simple versus complex tasks (with the passive task serving as the baseline). Inconsistent with Lalo et al.'s hypotheses, motor complexity did not appear to affect the ERPs for either group of participants. In addition, the identifiable ERP peaks were noted less reliably overall (for peaks such as the MMN, N2b, and P3b) for the adults with Down syndrome in relation to the typically developing participants, suggesting that the reliability of even simple sensory processing peaks might fundamentally differ between persons with Down syndrome and typically developing people of the same chronological age. The lack of reliable ERP peaks in this population suggests either a fundamental alteration of processing or could be related to the young mental ages of the participants, as the MMN continues to develop through middle childhood and adolescence (Bishop, Hardiman, & Barry, 2011), as do auditory ERPs more generally (Bishop, Anderson, Reid, & Fox, 2011). Furthermore, the lateralization of ERP components also changes with age, with auditory ERPs become more visible in central scalp locations with increasing age. Since Bishop et al. only recorded ERPs at midline central locations (Cz and Pz), their findings may be related to differences in the location of ERPs among individuals with Down syndrome whose cognitive abilities are less mature than among typically developing participants and whose ERPs would perhaps be larger at lateral electrodes than at central scalp location.

In the one study of olfactory ERPs among adults with Down syndrome in relation to CA-matched comparison participants, Wetter and Murphy (1999) found that individuals with Down syndrome had lower olfactory thresholds (poorer sensitivity to smell), as well as longer latencies to process smell in relation to typically developing participants. For both groups, detection threshold and ERP latency were correlated, and specifically in the group of participants with Down syndrome, higher ratings of dementia were related to longer latencies of the P3b component, suggesting that individuals with Down syndrome who had poorer cognitive functioning had a slower brain response to smell. Overall, sensory processing (visual, auditory and olfactory) appears to be more effortful for individuals with Down syndrome than CA-matched typically developing comparison participants.

Higher Order Processing Among Persons With Down Syndrome Despite the numerous studies of resting state fMRI, which provide information about brain anatomy and the brain's functional organization in the absence of task demands, we only found one fMRI study in which participants actively listened to speech and one in which individuals with Down syndrome completed some sort of experimental task that relates to cognition. Losin, Rivera, O'Hare, Sowell, and Pinter (2009) assessed brain activation patterns using fMRI while participants with Down syndrome and age-matched typically developing adolescent participants rested (control condition), or passively listened to speech presented forward and backward. The contrast of interest was between forward and backward speech, which would allow researchers to isolate the language-specific aspects of receptive language. The main finding was a significant difference in brain activations between forward and backward speech among the typically developing participants (temporal

language regions), but not for the participants with Down syndrome, suggesting that the latter group did not process the linguistic elements of the task.

In contrast to the passive listening approach of the previous study, Jacola et al. (2011) compared brain activations of adolescents and adults with Down syndrome and CA-matched typically developing participants while the participants completed a basic categorization task in which they were presented with pictures of animals one at a time and were asked to respond by button press to farm animals. Jacola et al. compared activations elicited by the categorization task to a control condition in which the participants pressed a button in response to the appearance of a scrambled image (simple detection) to isolate visual object recognition and semantic classification regions of the brain. In addition to the experimental task, the participants also completed the Peabody Picture Vocabulary Test (PPVT; a standardized measure of receptive vocabulary) as well as the Stanford-Binet V (SBV), a measure of IQ. The SBV scores reported reflect only scores on a composite of verbal and nonverbal visual-spatial subtests, which were correlated to the BOLD responses. Correlational analyses between the BOLD responses and the PPVT scores were not computed because of "more variability in the scores for the individuals with Down syndrome compared to those for the typically developing individuals" (Jacola et al., 2011, p. 349). Overall, the mean IQ of the typically developing participants was double that of the participants with Down syndrome, and, as might be expected, the performance of the participants with Down syndrome was much worse than that of the typically developing participants. However, these differences in performance were not correlated with PPVT or SBV scores suggesting that task performance was not related to underlying cognitive abilities. On the basis of these findings, Jacola et al. suggest that individuals with Down syndrome activated different brain areas than the typically developing participants to complete the task, that the relationships between SBV scores and areas of activation differed between the groups, and that activation differences could also reflect performance differences. The findings from this study are difficult to interpret because of small sample size, differences in cognitive abilities between the groups, as well as differences in thresholding requirements for inclusion of BOLD activations between the two groups of participants—for no specified reason, the inclusion practices were more liberal for the participants with Down syndrome than for the typically developing participants. Although a first step in the quest to understand differences in brain activations involving a task that requires cognitive processing, the findings from this study do not really provide any information other than to say that individuals with Down syndrome are different than CA-matched typically developing individuals.

This review highlights that we are only at the beginning stages of utilizing neuroscience approaches to complement the study of cognitive processing among persons with Down syndrome. Very few studies involved placing any cognitive demands on the participants, and none involved MA-matching. This is particularly troubling as Down syndrome is one of the most common etiologies of intellectual disability, with one of the better-understood cognitive phenotypes. In addition, the findings from all of these studies suggest that the defect approach permeates the literature on Down syndrome. As such, activations in the case of fMRI and neurophysiological responses in the case of ERPs are always considered defective, if they differ from that of typically developing participants who generally have double their IQs. Only Jacolo et al. (2011) even acknowledged that MA matching might help further our understanding of how and whether individuals with Down syndrome process information in different ways than typically developing individuals.

Persons With Williams Syndrome. As persons with Williams syndrome are characterized by a hypersocial phenotype and common visuospatial deficits that appear related to a difficulty integrating parts into wholes, neurobased studies of individuals with Williams syndrome have been focused on global-local stimulus processing ($n = 2$) or amygdala responses to different facial expressions ($n = 6$). Five of the studies reported here were completed by the same research group, headed by Ursula Bellugi and Allan Reiss, who have provided an extensive understanding of both Williams syndrome and of the role of the amygdala more generally. Their group seemed to consistently consider issues related to matching participants, either by assessing the effect of IQ on task performance and regions of interest, by directly matching participants on the basis of MA, or at the very least by acknowledging a lack of a comparison group as a limitation.

Global-local Processing in Williams Syndrome Both studies of global-local processing in Williams syndrome involved the presentation of Navon-type stimuli (Navon, 1977), composed simultaneously of global and local levels. The global level stimuli, typically letters or shapes, are made up of smaller, local level letters or shapes, which could either be congruent or incongruent with the global level (e.g., a large S made up of small s's or small o's respectively). Typically developing individuals generally show a

global precedent on these tasks, as they are faster and more accurate at detecting stimuli at the global level as compared with the local level, although this may vary as a function of stimulus characteristics (e.g., Enns & Kingstone, 1995; Kimchi et al., 2005). Mobbs et al. (2007) used fMRI to assess global–local processing of shapes among participants with Williams syndrome and CA-matched typically developing participants. The participants were asked to attend only to the big shapes and to press one button if the big shape was a triangle and a second button if the big shape was a square. Thus, in this case, the local level of the stimulus was never mentioned to the participants. Comparisons were made between BOLD and performance responses on this experimental task with a control task in which shapes were presented without local elements (e.g., a big triangle and a big square). Mobbs et al. found that the participants with Williams syndrome were less accurate and marginally slower than the typically developing participants, but these results did not seem to be linked to IQ. Activation differences were diffuse, with areas of larger activation among the participants with Williams syndrome in the dorsolateral prefrontal cortex, which Mobbs et al. linked to increased effort required to perform the task. Less activation was seen in parietal and early visual cortical areas among the individuals with Williams syndrome, suggesting disruptions in the dorsal-stream pathway.

Key and Dykens (2011) compared the performance of participants with Williams syndrome with typically developing participants matched on the basis of CA. The participants were asked to respond yes or no (by button press) with respect to the presence of the letter H, which could appear either at the local level (an S made up of small h's) or the global level (an H made up of small s's) with equal probability (20% each) during concurrent ERP recordings. The remaining 60% of trials were non-target standards (which did not contain the letter H). The presentation of only 30 target trials (30 global and 30 global stimuli) is problematic as it is a very low number of trials for an ERP study, which requires multiple repetitions to reduce the signal to noise ratio. Four components of interest were tested for between and within group effects. Early components included the occipital P1 (between 70 and 150 ms) and the N150 (between 150 and 220 ms), whereas later components of interest included the centro-parietal P3b (between 300–600ms) and the frontal P3a (between 200 and 400 ms) based on other ERP studies of global-local processing.

As expected, the typically developing participants demonstrated a global precedent behaviorally as evidenced by faster responses to the global stimuli than both the local and the distractor stimuli, but were equally accurate across stimulus types. ERP components were significantly different among the standard, local, and global level stimuli at the N150, and P3a and b components. Global and local targets elicited more negative N150s than standards, and more positive P3a and b amplitudes. No differences were noted between the physiological responses to global and local targets. Among the participants with Williams syndrome, no global precedent was noted although the global targets were detected more accurately than the local targets (75% vs. 31% approximately). ERP differences were noted for the early N150 and P1 components. P1 amplitudes were lower for the global versus the standard targets and had a shorter latency. The N150 component was more negative (larger) for the global versus the standard stimuli. Further, later in the processing stream, the global targets elicited a larger and earlier P3a component relative to standard stimuli. Although these findings suggest that individuals with Williams syndrome detect the global configuration of Navon stimuli similarly to typically developing participants early in the processing chain, additional analyses would have allowed for stronger conclusions. One, the groups were never compared with one another, so group differences or interactions between the conditions and group were never assessed. Two, the processing of local targets was not compared directly with the processing of global targets, which would have also allowed for an understanding of the relative physiology underlying global–local processing. Three, the participants with Williams syndrome were compared with college students who, even if their IQs were not assessed, can be assumed to function at a significantly higher cognitive level. Key and Dykens made no attempt to correlate task performance with IQ as a function of condition, nor did they take into account the obvious IQ differences between the groups in their analyses of ERPs or in their discussion (other than to say that IQ matching might be a useful future direction). Although this study provides evidence that early visual processing of global configurations seems typical in Williams syndrome, this study, as with the one by Mobbs et al., does not allow for an examination of the relations between global and local processing. Without actual comparison of these levels of processing, much remains to be learned about the nature of global-local processing among persons with Williams syndrome.

Facial Expression Processing and Face Processing in Williams Syndrome To better understand the hypersociability in this group, Haas et al. (2010) used fMRI to assess the relationship between amygdala responses to different facial expressions (happy, fearful, neutral and control images that were scrambled) among adults with Williams

syndrome. The participants' parents completed a questionnaire used to assess their adult child's sociability across three scales (global sociability, approach strangers, and approach familiars). In the experimental task, the participants who were in the fMRI portion of the experiment were asked to respond by a button press as to whether the image they were presented was male, female, or scrambled (three buttons). The goals were to look at the associations among task performance, BOLD responses in the amygdala, and parental reports of sociability. Behavioral findings indicated no relationship between task performance (reaction time and accuracy) and the parental reports of sociability. However, consistent with the notion that the increased social approach of individuals with Williams syndrome is related to a decreased response to social fear, Haas et al. found that a diminished amygdala response to fearful faces was associated with a greater tendency (as reported by parents) to approach strangers. This is initial evidence of a neural correlate of behavioral observations of hypersociability, and provides a developmental pathway that may lead to this behavioral phenotype.

In a further attempt to understand the relationship between hypersociability and amygdala responses, Paul, Snyder, Haist, Raichle, Bellugi, and Stiles (2009) compared the performance and associated BOLD responses of individuals with Williams syndrome as well as a group of typically developing participants matched on CA and a group of younger typically developing children matched to the participants with Williams syndrome on the basis of MA on a facial expression matching task. The participants completed an experimental task in which they were required to determine whether a target face matched either of two faces presented just prior to the target. This task was completed both in and out of the scanner with slight modifications. Behaviorally, prior to the scanning, the performance of the individuals with Williams syndrome was as fast and as accurate as the MA-matched typically developing children, and both of these groups were slower and less accurate on the task than the CA-matched typically developing participants. However, while performing the task in the scanner, the MA- and CA-matched participants outperformed those with Williams syndrome with respect to both reaction time and accuracy. With respect to BOLD responses, the physiological responses to the task were in many ways similar between the participants with Williams syndrome and the MA-matched group, whose activation patterns were less robust than the CA-matched participants. The exception to this was the amygdala, which was more active in both the MA and CA groups than among the participants with Williams syndrome. The finding of an underactive amygdala is consistent with Haas et al.'s (2010) finding that decreased amygdala responses to fearful faces are associated with a greater tendency to approach strangers.

Haas, Mills, Yam, Hoeft, Bellugi, and Reiss (2009) used both ERPs and fMRI to test the neural basis of social responsivity among individuals with Williams syndrome in response to emotionally valent facial expressions (happy and fearful). In both the ERP and the fMRI studies, the participants were asked to detect whether the images that were presented were male, female or scrambled by pressing one of three response buttons. The face stimuli depicted happy, fearful or neutral facial expressions. Fourteen participants with Williams syndrome completed the fMRI study and their performance was compared with that of typically developing individuals matched on the basis of CA, while 30 participants with Williams syndrome completed the ERP study (11 overlapped) and their performance was compared with typically developing participants matched on CA and to a smaller group of participants with idiopathic developmental delay (participants who had an intellectual disability of unknown origin and were not autistic) matched on the basis of full scale IQ (test unspecified). The age range of the IQ-matched participants groups were similar, though the authors did not mention that they specifically match on CA. Behaviorally, the performance of the participants with Williams syndrome was slower and less accurate than the CA-matched typically developing participants but did not differ from the IQ-matched participants with idiopathic developmental delay. The fMRI findings indicated that compared with CA-matched participants, the participants with Williams syndrome showed increased right amygdala activation for happy as compared with neutral facial expressions, and lower right amygdala activation than the typically developing participants when the fearful facial expressions were compared with the scrambled images. Neither IQ, reaction time, nor accuracy accounted for their findings.

With regard to the ERP paradigm, Haas et al., (2009) compared differences between happy and neutral facial expression as well as fearful-neutral facial expressions in three time periods (N200, P300–500 and P500–700). At 200 ms, they found that the participants with Williams syndrome showed a larger difference between fearful and neutral facial expressions than the MA-matched participants and a trend for the same finding among the CA-matched participants (but only the participants with Williams syndrome showed a smaller response to fearful facial expressions relative to neutral ones). Between 300 and 500 ms, the participants with Williams syndrome

demonstrated greater physiological responses (larger differences between happy and neutral expressions) relative to both the CA- and MA-matched groups (which did not differ from each other). Between 500 and 700 ms, there was a larger difference between physiological responses to fearful—neutral facial expressions in the CA-matched participants relative to the participants with Williams syndrome. The Williams syndrome and MA-matched groups did not differ in their responses at this time point. Together, these findings corroborate the notion that individuals with Williams syndrome show a decreased response to fearful facial expressions, which is visible early in the processing stream and which appears to be maintained in more cognitive time frames (between 500 and 700 ms). The participants with Williams syndrome also showed increased reactivity to happy facial expressions as measured by both fMRI and ERPs. These findings map well onto the behavioral phenotype of individuals with Williams syndrome who are often very socially driven but also approach others indiscriminately, although the significance of these findings are diminished considerably due to the use of two problematic groups—CA-matched typically developing persons and an etiologically unspecified group of persons with intellectual disability.

Another explanation of the unique social characteristics of persons with Williams syndrome is linked to the finding that they rate pictures of faces as more approachable than MA-matched comparison participants (Frigerio et al., 2006), a phenomenon that Bellugi, Adolphs, Cassady, and Chiles (1999) termed a positive attribution bias. In an attempt to understand this positive attribution bias, Mimura et al. (2010) assessed activations of the amygdala and the orbitoprefrontal cortex (OFC), which are involved in facial affect recognition among seven participants with Williams syndrome and seven typically developing participants matched on CA. The participants completed a facial expression-matching task by responding with a button press as to whether two faces presented side by side had matching or mismatching facial expressions while in the scanner. Specifically, Mimura et al. attempted to assess the role of both the medial and lateral portions of the OFC, which play different roles in facial expression recognition. The medial regions of the OFC are involved in monitoring the reward value of reinforcers, whereas the lateral OFC is involved in the monitoring of punishers. Mimura et al. hypothesized that among typically developing individuals, positive facial expressions would activate the medial OFC while negative facial expressions would activate the lateral OFC. In contrast, they expected that among individuals with Williams syndrome, facial expressions depicting both positive and negative facial expressions would activate medial regions as a result of their positive attribution bias. Accuracy on the task did not differ between the groups despite IQ differences (although *p*-values increased when FSIQ was used as a regressor).

Mimura et al.'s (2010) fMRI findings indicated that the participants with Williams syndrome had decreased activation in the right amygdala and right lateral OFC relative to the typically developing participants for negative facial expressions but the right medial OFC showed greater activation than the typically developing participants in response to negative stimuli (compared with positive stimuli). Although no relationship between task performance and IQ were found at the level of the whole brain, when region of interest analyses were repeated in the participants' native space, a correlation was found between right lateral OFC activation and IQ for the positive versus negative contrast among the individuals with Williams syndrome, suggesting that those individuals with higher IQs also had larger activation differences between positive and negative facial expressions in this region than those with lower IQs. These findings are consistent with previous evidence of decreased amygdala responses to negative facial expressions among persons with Williams syndrome as compared with typically developing individuals, but are novel with regard to the finding that that negative facial expressions activate regions of the brain associated with reward gating in individuals with Williams syndrome compared with typically developing participants. This suggests that these two regions might work in tandem to explain why individuals with Williams syndrome tend to approach strangers. That is, individuals with Williams syndrome view negative facial expressions as rewarding, and also show a decreased fear response to negative facial expressions.

Thronton-Wells, Avery, and Blackford (2011) also attempted to dissect the role of the amygdala among individuals with Williams syndrome by comparing BOLD responses to social and non-social images among participants with Williams syndrome relative to comparison participants with an inhibited temperament group (who have high non-social fear responses, which is consistent with the Williams syndrome phenotype) and those with an uninhibited temperament who are characterized (similarly to individuals with Williams syndrome) as being highly sociable. Thus, they attempted to determine whether the typical findings related to amygdala responses among persons with Williams syndrome are unique and specific to this group or rather more characteristic of the personality traits associated with the phenotype. Their findings indicated that individuals with Williams syndrome had

larger BOLD responses to non-social fear images than the typically developing individuals with a similar level of fear. With respect to social images, the BOLD response in the amygdala of individuals with Williams syndrome was commensurate with that of typically developing individuals who are highly social, suggesting that high sociability personality traits might explain more generally the heightened amygdala responses rather than being unique to individuals with Williams syndrome.

In addition to the role of the amygdala and the OFC in facial expression processing, and thus in the hypersociability of individuals with Williams syndrome, the fusiform face area is also an important region associated with the identification and recognition of faces. As individuals with Williams syndrome have been found to have face-identity recognition abilities that are commensurate with CA and better than would be expected for MA (Bellugi, Lichtenberger, Jones, Lai, & St George, 2000), the fusiform face (FFA) area might be involved in Williams syndrome. In one example, Golarai et al. (2010) systematically deconstructed the role of the FFA (and the relationship between task performance, IQ and FFA activation) among individuals with Williams syndrome and CA-matched typically developing comparison participants on a passive viewing task in which the participants were presented with grayscale images of faces, objects, textures and places. They sought alternative explanations to their finding that the FFA of individuals with Williams syndrome is almost double the volume of the FFA of typically developing participants by using different thresholds, clustering and spatial smoothing techniques, and comparing their FFA results to other brain areas associated with face processing. The participants also completed a face recognition task outside of the scanner and, consistent with previous findings, performance on the task did not differ between typically developing participants and those with Williams syndrome, although a significant correlation between size of the right FFA and task performance was found among the participants with Williams syndrome but not among the typically developing participants. This correlation remained significant even after IQ was controlled (despite task performance being correlated with IQ), thereby providing a neural anatomical correlate that might explain why individuals with Williams syndrome have better facial recognition abilities than would be expected for their MA.

Summarizing Neuroscience Work Across Etiologies. Our review of neuroscience-based studies across etiological groups highlights that we are in the most nascent stages of work in this area. The studies were generally characterized by essential methodological problems either in their execution, or in their consideration of cognitive level in their findings, thereby considerably diminishing the conclusions that can be made.

Although the study of intellectual disability within the context of neuroscience is still a new area of inquiry, several foundational questions have been raised, especially with regard to the roles of developmental level, CA, and specific etiology on ERP and fMRI findings. We have no methodological consensus regarding how best to treat IQ, or cognitive development more generally, nor do we have a real understanding of their relation to brain physiology. Further, the difficulties in recruitment and retention of participants with an intellectual disability for studies involving fMRI and ERPs necessitate that the most of the studies involve adult participants, which represents the endpoint of development, leaving open an important chicken-egg problem. That is, what is the degree to which neural differences are causes or consequences of the behavioral phenotype? Nonetheless, as more researchers with different areas of expertise work together, we hope that these questions as well as those regarding the relationship between brain and behavior in intellectual disability will be addressed.

The current advancement of technology and the related increased access and funding available to researchers using neuroscience tools to study persons with intellectual disability are certainly welcome contributions to this field, but have given rise to a new generation of defect theorists who, in their frantic pursuit to identify key neurological problems, lay waste to many of the tenets of developmental theory and methodology. Thus, decades after its apparent demise, the defect approach appears to be rearing its head again. We are a long way from being able to consider the whole person from a neuroscience perspective but we hope that by promoting the importance of developmental theory and methodology that we will accelerate the developmental legitimacy of neuroscience research in the study of intellectual disability.

CONCLUSIONS

From Genes to Brain to Behavior in Intellectual Disability: Future Directions in Research

More than 10% of the human genome has been implicated in intellectual disability, both organic and familial (Schuurs-Hoeijmakers et al., 2013). The number of well-known syndromes associated with intellectual disability is quite small, however a major advancement of the

twenty-first century is the mapping of these known genetic disorders to neural consequences. This approach has led to breakthroughs in understanding exactly how specific genes work together to build a brain. The burgeoning field of epigenetics is also beginning to shed light on the subtle influences of external factors, from diet and the prenatal environment, to parenting. Each child enters their individual world, with their unique epigenome, acting upon and eliciting experiences from the world that combine to carve the child's unique developmental path, like water carving a stream in the sand. Just as every child carves out a unique developmental pathway, some are more functionally adaptive than others. Thus, the orthogenetic principles and similar-sequence/similar-structure hypotheses are still relevant to understanding both familial and organic intellectual disability, as are Piagetian constructivism, and the neo-Piagetian neuroconstructivist (Karmiloff-Smith, 1998) models in which the child, typically developing or otherwise, is the unique product of cumulative and self-driven experiences. Via general and universal developmental principles, the unique child constructs his or her own path through the selection of experiences and evocations from the environment. The biology of the child presents merely a set, albeit often a powerful one, of constraints.

Summary

Throughout this chapter, we highlight, that, as with all developmental processes (Werner, 1957), the development of the developmental approach to intellectual disability led to an essential deconstruction, in this case of the commonly applied theories and methodologies in the field, as part of the progression toward a more precise but comprehensive understanding. Thus, this deconstruction is not one of a Humpty Dumpty who can never again be put together. Rather it is one of a chrysalis in which the ideas are even more beautiful and lofty than the original. This optimism is based in the advances in the almost half century since Zigler's original articulation of the developmental approach to intellectual disability and in the twenty-first century sophistication in experimental technology and empirical methodology in the study of genetics, brain functioning, behavior, social and interpersonal functioning, and emotional well-being, as well as in the study of the complex developmental trajectories and relations among them. Through this synergy, the key to understanding the development and functioning of the heterogeneous grouping of persons labeled as intellectually disabled is with the paradoxical top-down imposition of developmental theory on the bottom up process of piecing together a mosaic based on fine-tuned and precise empirical evidence from relatively precise homogeneous groupings. Despite, and because of, the abandonment of the big stories of the defect and related approaches to intellectual disability, we now know much more about persons with intellectual disability than we have in the past, but are also painfully aware of the extent to which we only tap the surface of all there is to know. As we (Burack et al., 2012) noted elsewhere, the outcome of this process might best described by yet two more paradoxes, that the more we know, the less we know, and that is still progress, because, the less we know we know, the more we (really) know. Accordingly, despite all the advances in research on persons with intellectual disability since the Hodapp and Burack (2006) chapter in the last edition of this handbook, we can make the same claim that we are only in the early stages of the development of the developmental approach to intellectual disability and are still just becoming more aware of the immensity of the task ahead of us—but that is the nature of a developmental process.

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CHAPTER 2

Fragile X Syndrome as a Multilevel Model for Understanding Behaviorally Defined Disorders

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INTRODUCTION

Neurodevelopmental disorders of known genetic origin, like fragile X, Williams, and Down syndromes, can serve as multidisciplinary, multilevel models for understanding the neurodevelopmental mechanisms and the origins of other disorders that are currently defined only at the behavioral level (e.g., dyslexia, attention-deficit/hyperactivity disorder [ADHD]; autism spectrum disorder [ASD]), with one critical proviso: they are considered within a truly developmental framework. Indeed, special emphasis will be given throughout this chapter on the importance of the developmental perspective on neurodevelopmental disorders. It is crucial for researchers always to recall that early genetic modifications—whether deletions, translocations, duplications, or mutations—are likely to affect neurocognitive functioning from the very outset of development and to have complex interactions and widespread cascading effects over time on the resulting phenotype. For example, research on infants with disorders of known genetic origin has highlighted the importance of investigating empirically the very early developmental profile of each syndrome during infancy, rather than assuming a priori that the cognitive profile in adults is representative of earlier deficits and abilities (Karmiloff-Smith, 1998; Paterson, Brown, Gsödl, Johnson, & Karmiloff-Smith, 1999). So, researchers always need to keep in mind a clear distinction between the mature, developed, relatively stable brain and the dynamically changing developing brain (Karmiloff-Smith, 2010). Thus, while genetic disorders can provide unique insights into how relatively well understood genetic modifications, molecular pathways, and systems neuroscience influence cognition, these complex interactions cannot be fully understood outside their developmental context (Doherty, Shimi, & Scerif, 2015).

In this chapter, we take the case of one such neurodevelopmental disorder of known genetic origin, fragile X syndrome (FXS), to discuss a number of broad issues that emerge from the comparison with disorders that are behaviorally defined (see Farran & Karmiloff-Smith, 2012, for a similar approach using Williams syndrome as the model disorder). First, we provide a short summary of the genetic, neurocognitive, and behavioral characteristics of FXS, with special emphasis on the complex interplay between developmental stability and developmental change. Second, using longitudinal data, we discuss the ostensibly surprising fact that despite being a monogenetic disorder, there are wide within-syndrome individual differences in the phenotypic outcomes of individuals with FXS. The longitudinal findings highlight the existence of within-syndrome developmental trajectories that diverge over time as well as the importance of identifying both risk and protective environmental factors that influence these outcomes. Then we focus on cross-syndrome comparisons

of the similarities and differences in social and cognitive problems of children with FXS with those of children with two behaviorally defined disorders, ADHD and ASD. We conclude with a strong emphasis on the usefulness of cross-syndrome comparisons and a discussion of how this approach can be used as a model for understanding other genetic disorders in which within-syndrome variability has not been as thoroughly investigated, particularly within a longitudinal framework.

THE FRAGILE X GENOTYPE AND PHENOTYPE

Genetically, FXS is caused by the silencing of a single gene on the X chromosome, and in males who are carriers of the full mutation it results in an almost complete absence of the protein product linked to this gene in typical development. Phenotypically, the syndrome is associated with significant attentional, memory, and sociocognitive deficits that turn out to be more severe than would be predicted given levels of overall developmental delay. This therefore makes FXS an ideal model in which to study the effects of protein networks on the developmental trajectories of attentional control and memory at multiple levels, from the cellular to the systems and cognitive neuroscience, and how they impact on specific cognitive domains such as social cognition (see Belmonte & Bourgeron, 2006; Bourgeron, 2009; Scerif & Karmiloff-Smith, 2005, for a discussion of this interdisciplinary approach). Nonetheless, at all levels, scientists must take into account the developmental constraints acting over time if we are to reach a full understanding of the resulting phenotype. In the following paragraphs, we characterize FXS at these different levels.

Constituting the most common inherited form of intellectual disability, FXS has a prevalence of approximately 1 in every 4,000 males and 1 in every 8,000 females, although more recent figures estimate a general prevalence closer to 1 in 2,500 (Crawford, Acuña, & Sherman, 2001; Hagerman, 2008). It results from a large trinucleotide CGG repeat expansion in the 5' untranslated region of the *FMR1* gene at site Xq27.3. While typically developing individuals usually have approximately 30 CGG repeats at this site, premutation carriers present with around 55–200 repeats, and individuals with the full mutation have over 230 repeats (Maddalena et al., 2001). In this chapter, we will concentrate on full mutation carriers because of the greater wealth of developmental findings to date (but see Bourgeois et al., 2009; Cornish, Kogan, Li, Turk, Jacquemont, & Hagerman, 2009; Cornish et al., 2008; for fascinating research that now reveals unsuspected impairments also in premutation carriers, and their developmental progressions from childhood into young and late adulthood). The extensive CGG repeat expansion in full mutation carriers gives rise to epigenetic changes, such as methylation of the *FMR1* gene promoter, and thus transcriptional silencing of the *FMR1* gene itself, which then results in a reduction of FMRP, the fragile X mental retardation protein (Verkerk et al., 1991). Because of the location of the *FMR1* on the X chromosome, males are usually more severely affected than females, the latter being more resilient because they have two X chromosomes, only one of which is randomly inactivated (Grigsby, Kemper, Hagerman, & Myers, 1990).

Phenotypically, individuals with FXS present with a number of physical features: prominent ears, a long narrow face, flat feet, joint laxity, and macro-orchidism (Hagerman, Van Housen, Smith, & McGavran, 1984). However, while these features are not especially obvious in early development, they become more evident with growing maturation. By contrast, developmental delay in cognitive and motor milestones is more obvious during the early stages of development, and is often what alerts clinicians to the possibility of a neurodevelopmental disorder in families with newly diagnosed children and no previous FXS births (Bailey, Skinner, Hatton, & Roberts, 2000). By contrast, given the inherited nature of the syndrome, if there is already an older child with FXS in the family, babies are screened for FXS during fetal or early postnatal life even in the absence of overt physical signs.

In terms of cellular modifications, FXS results in numerous anatomical and functional changes at the level of synaptic connectivity. Post-mortem studies have identified immature dendritic spines in neurons (Hinton, Brown, Wisniewski, & Rudelli, 1991; Rudelli et al., 1985). Interestingly from an evolutionary perspective, the *FMR1* gene has high conservation across species (Verkerk et al., 1991), which has made it possible for animal models to investigate in greater depth the changes that arise from the loss of FMRP. For example, *Fmr*1 knockout mice develop dense, immature dendritic spines that are very similar to those observed in human patients (Comery et al., 1997; Grossman, Aldridge, Weiler, & Greenough, 2006). Additional murine research has revealed that FMRP binds selectively to mRNA in the postsynaptic spaces of dendritic spines, thereby repressing synaptic translation by stalling ribosomal translocation. In typical development, FMRP derepresses translation in response to synaptic activity, making the synthesis of crucial synaptic plasticity proteins possible. The FXS loss of FMRP thus constrains this response and, because deficits in synaptic plasticity

correlate with memory and learning problems, it has been argued that such deficits are the main cause of the resulting FXS phenotype. In particular, mGluR dependent long-term depression (LTD), a major form of synaptic plasticity, is thought to constitute the impaired neurological pathway involved in the FXS behavioral symptoms (Bear, Huber, & Warren, 2004). Furthermore, it has been demonstrated that mGluR LTD is indeed altered in *Fmr1* knockout mice (Huber, Gallagher, Warren, & Bear, 2002), and that mGluR antagonists can indeed enhance cognitive and behavioral outcomes (Yan, Rammal, Tranfaglia, & Bauchwitz, 2005), as well as rescuing immature dendritic spine morphology (Michalon et al., 2012; Nakamoto, Nalavadi, Epstein, Narayanan, Bassell, & Warren, 2007). The successes of the murine intervention studies with these antagonists have now resulted in relatively successful clinical trials with human patients using drugs to target the mGluR LTD pathway (Berry-Kravis et al., 2009). However, while atypical synaptic function and anatomy are characteristic of most animal models of FXS, an examination of different studies that have used *Fmr1* knockout mice reveals that these synaptic phenotypes are in fact transient and appear developmentally only within short time windows. This means that their effects are dependent upon the temporal expression of *Fmr1* (Meredith, Dawitz, & Kramvis, 2012), stressing again the importance of a developmental perspective on such questions. In sum, although there is a single and well-understood genetic cause of FXS, there is wide variation in phenotypic outcome in this population. This is likely to be due to a combination of individual temporal expression dynamics together with differing timing of environmental impacts, something to which we will turn our attention in a subsequent section.

BRAIN–BEHAVIOR RELATIONS IN FRAGILE X

The investigation of human patients with FXS at the systems level has yielded interesting links between genes, brain, and behavior. For example, memory impairments, particularly working memory, correlate with FMRP levels in FXS as well as with abnormal brain activation in regions that are critical for memory functions (Menon, Kwon, Eliez, Taylor, & Reiss, 2000). Moreover, during attention and impulse control tasks, FMRP also has been shown to correlate with the atypical recruitment of dorso-striatal networks (Hoeft, Hernandez, Parthasarathy, Watson, Hall, & Reiss, 2007; Menon, Leroux, & White, 2004). These studies tend to lend support to the hypothesis that FMRP is required for the brain to react rapidly in the service of executive function and working memory tasks (Lightbody & Reiss, 2009). Additionally, evidence is accruing to suggest that reduced FMRP is associated with reduced amygdala volume as well as reduced amygdala activation during emotion processing tasks (Hessl et al., 2011). Furthermore, recent research with mouse models suggests a general neural imbalance between excitation and inhibition across the whole brain in FXS (D'Hulst et al., 2006; Gibson, Bartley, Hays, & Huber, 2008). An exciting area of open research would be to investigate such an imbalance in humans by measuring the levels of excitatory and inhibitory neurochemicals, such as GABA and glutamate, in individuals with FXS using magnetic resonance spectroscopy. These findings point to a serious problem in individuals with FXS, because it is known that the excitatory/inhibitory balance is critical for optimal functioning at the neural level, both in terms of region specificity and across developmental time.

Much of the early research on the FXS brain was done on older children and adults, but recently structural imaging studies have targeted very young children with the syndrome (Haas et al., 2009; Hoeft et al., 2008, 2010, 2011). This should in time make possible the much earlier diagnosis of FXS, identifying in infants precocious neural markers of atypical brain development. For example, in a longitudinal study by Hoeft and collaborators (2010) on 1–3-year-old boys with FXS, gray and white matter volumes were measured over a 2-year period. The researchers identified areas of the brain in which gray matter volumes were either enlarged (caudate, thalamus, and fusiform gyri) or reduced (cerebellar vermis), and this held across both time points, thereby highlighting from a very early point in development quite stable regional effects in the brains of individuals in this population. Interestingly, other brain regions revealed initial gray matter volume that was similar to that of typically developing controls (orbital gyri, basal forebrain, and thalamus), but which subsequently increased in size in FXS, again stressing the need for a developmental perspective when considering the atypical brain (Karmiloff-Smith, 2010). In contrast to gray matter volumes, white matter volumes of fronto-striatal regions were greater in FXS compared with typically developing controls at the first time point, and, in this case, the differences did not remain stable but increased over time. In general, then, these results underscore how structural (and probably functional) abnormalities within different brain regions develop differently over time in FXS, reflecting again time-dependent effects of *FMR1* silencing. Such effects are very similar to those already highlighted in the context of murine models of FXS.

COGNITIVE AND BEHAVIORAL PATTERNS IN FRAGILE X

Individuals with the full FXS mutation present with a very characteristic cognitive and behavioral profile across development, despite the existence of strong individual variation. Males are usually severely impaired intellectually, with an average IQ as low as 41, whereas those males with incomplete *FMR1* inactivation can turn out to be less affected (Merenstein, Sobesky, Taylor, Riddle, Tran, & Hagerman, 1996). Males also have quite severe communication difficulties, including significant language delay coupled with social awkwardness alongside hyperactivity, inattention, impulsivity, and anxiety. By contrast, females—even those with the full mutation—tend to present with less deficits (due to their unaffected second X chromosome), often having only moderate and in some cases no intellectual impairment at all. However, social problems are frequently part of the female FXS phenotype, but unlike the co-occurring symptoms in males with FXS, social impairments in girls and women are more likely to be accompanied by anxiety or depression (Freund, Reiss, & Abrams, 1993).

Noteworthy is the fact that subtle behavioral and cognitive delays and deficits are evident in infancy, with parents becoming concerned about their children's symptoms on average as early as 9–13 months of age. However, clinical confirmation of the atypical developmental pathways often has to wait until the child is considerably older, that is, on average around 21–24 months of age, with in many cases a full diagnosis of FXS not happening until as late as 32–35 months of age (Bailey, Skinner, Hatton, & Roberts, 2000; Bailey, Skinner, & Sparkman, 2003). The early signs at around 9–12 months of age include decreased object play, increased leg stereotypies, and atypical postures. In fact, these quite subtle symptoms have been shown actually to be able to yield a FXS diagnosis in infancy with some 73% accuracy (Baranek et al., 2005). Furthermore, scientific research has revealed that already in infancy, those with FXS demonstrate poor response inhibition (Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004, 2007), poor saccadic eye-movement control (Scerif, Karmiloff-Smith, Campos, Elsabbagh, Driver, & Cornish, 2005), and prolonged visual attention to objects or what is known as sticky fixation (Roberts, Hatton, Long, Anello, & Colombo, 2012). In subsequent FXS development, school children and adolescents also display poor response inhibition (Sullivan, Hatton, & Hammer, 2007) and atypical patterns of visual attention (Hooper, Hatton, & Baranek, 2000; Munir, Cornish, & Wilding, 2000a, 2000b). Finally, executive function is clearly deficient in FXS in childhood, with concomitant memory impairments (Lanfranchi, Cornoldi, & Drigo, 2009). All of these characteristic problems continue into adulthood; nonetheless, the most serious cognitive impairments have been shown to reside in executive function and visual-spatial attention in this syndrome (Cornish, Munir, & Cross, 2001).

INSIGHTS FROM LONGITUDINAL STUDIES OF FRAGILE X

Attentional control has been a particular area of FXS research, but hitherto mainly only in cross sectional designs. Here, we provide data from a longitudinal approach that yielded deeper insights into the FXS phenotype. It is indeed longitudinal research that has highlighted two crucial factors affecting the cognitive phenotype of individuals with the full mutation. The first concerns differences in attentional biases that tend to alter cognitive development from the very outset for children with this genetic disorder. One important way of targeting the attentional domain is to compare younger and older individuals with FXS (Cornish et al., 2007; Scerif et al., 2004, 2005, 2007), and especially to do so within a longitudinal design (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2012; Cornish et al., 2013; Scerif, Longhi, Cole, Karmiloff-Smith, & Cornish, 2012). The second resides in the fact that, as we mentioned earlier, even in seemingly simple monogenic disorders like FXS, the resulting phenotype displays significant phenotypic variability across individuals, as for instance demonstrated by studies of individual differences in saccadic eye-movement control in young children with FXS between 12 and 36 months of age (Scerif et al., 2005). Moreover, variability also exists in how abilities actually change longitudinally over developmental time in FXS (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2013; Cornish et al., 2012; Scerif et al., 2012). There is clearly no simple one-to-one mapping between the mutated gene and the resulting phenotype.

Noteworthy is that fact that studies of neurodevelopmental disorders have produced a new emphasis on theory development, highlighting the need to go beyond group comparisons and trace instead domain-specific or even task-specific developmental trajectories, by plotting, say, numerical or linguistic functioning against individuals' verbal or nonverbal ability levels (e.g., Thomas, Annaz, Ansari, Scerif, Jarrold, & Karmiloff-Smith, 2009). Basically, this involves a new focus on within-syndrome individual differences. There is indeed a glaring absence

of studies tracking change over developmental time, that is, longitudinally. For example, even though striking attentional difficulties had already been demonstrated in children with FXS, even when compared with a much younger typically developing group of children matched on overall developmental level (Cornish et al., 2007; Scerif et al., 2004, 2005, 2007), the cross sectional design did not make it possible to ascertain whether the severity of attentional difficulties increased over developmental time or remained stable. This was because the experimental instruments available to measure attention in younger and older individuals were often very different in nature and the outcomes across age were difficult to compare directly. Moreover, although the FXS cognitive phenotype has been extensively examined via cross sectional research, far fewer studies have probed longitudinal changes not only within attention but also in terms of other sensory and cognitive domains (e.g., Baranek et al., 2008; Roberts et al., 2009; Skinner et al., 2005). In other words, studies that simultaneously target the FXS phenotype both longitudinally and in a cross-domain design have been sadly lacking.

However, very recent research using the longitudinal approach has yielded new insights. For example, although we know that significant delays in attentional control are present in boys with FXS, this turns out not to be a case of developmental arrest. Instead, dynamic trajectories of delayed development have now been identified. For example, using a combined cross sectional and prospective longitudinal design, we examined early profiles of attention and working memory impairment in FXS (Cornish et al., 2013). When investigated only in cross sectional designs, significant weaknesses emerged for boys with FXS, with no clear improvement over chronological age. By contrast, when we examined the same issues in a longitudinal design, we were able to reveal that, although clearly impaired, the improvements that occurred over time in boys with FXS paralleled the slope of improvement that we witnessed in typically developing children. In other words, while cross sectional approaches would have called on an interpretation of developmental arrest, the longitudinal studies yielded developmental improvements, albeit delayed compared with TD controls, in both attention and working memory. While confirming previous cross sectional findings of deficits in attentional control and working memory compared with what would be expected given their general level of developmental delay, the Cornish and collaborators' longitudinal study (2013) additionally revealed improvements over developmental time that a simple cross sectional comparison would have masked. The longitudinal study also measured other aspects of the FXS cognitive profile (i.e., nonverbal intelligence) and revealed unique insights that would again have been missed in cross sectional approaches. For instance, cross sectional studies of nonverbal IQ scores, measured by the Leiter International Performance Scale–R (Roid & Miller, 1997), had tended to point to a potential plateau or even decline with age, whereas our longitudinal trajectories measured with growth scores (an analogue of raw scores that takes into account repeated presentations and item difficulty) highlight instead an albeit small yet significant improvement over developmental time (Cornish et al., 2012).

What about lower level perceptual rather than cognition-level functions? Are these unimpaired in FXS? Studies with adults (Van der Molen et al., 2012) and also with infants with FXS (Farzin, Whitney, Hagerman, & Rivera, 2008) suggest that visuospatial attention impairments may in fact be underpinned by atypical lower level perceptual abilities. Again, longitudinal data are crucial in evaluating whether low level perceptual processing differences do in fact lead over developmental time to atypical higher level processing. This yet again highlights the need for more longitudinal approaches to understanding the complexities of neurodevelopmental disorders like FXS.

In addition to the aforementioned striking group-level deficits, clinicians working with individuals with FXS tend to identify striking individual differences in attention outcomes, with some individuals much more seriously affected by inattention than others, even when they have equivalent levels of IQ. Again, longitudinal studies following sufficiently large samples could start to dissect the within-syndrome FXS variability, because they enable researchers to go beyond correlational measures, and ask instead how within-syndrome variability predicts subsequent outcomes. This was indeed our approach in the longitudinal study referred to above. We measured visual, auditory, and multimodal attention in young boys with FXS, aged between 4 and 10 years of age at time 1 and again 12 months later at time 2 (Scerif et al., 2012). We also assessed behavior in these boys through standardized teacher questionnaires targeting dimensions that are relevant to symptoms of ADHD (e.g., Conners Teacher Rating Scales; Conners, 1997). The results showed that the children with FXS attended less well than mental-age matched typically developing boys and had greater difficulties with auditory stimuli than with visual ones. In addition, unlike typically developing children, the boys with FXS did not benefit from multimodal information. Importantly from the perspective of individual differences, early visual attention markers in boys with FXS were significant predictors of their later ADHD symptomatology, highlighting the

need to identify the drivers of differing developmental trajectories for individual children within this seemingly homogeneous group if measured cross sectionally. Interestingly, while visual attention was a significant longitudinal predictor of ADHD symptoms in the boys with FXS (Scerif et al., 2012), it was auditory attention that predicted later symptoms related to ASD (Cornish et al., 2012).

THE CHALLENGES OF COMORBIDITY

Individuals with FXS present with a particularly high risk for comorbid symptoms, which are found in autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Indeed, some 50–90% of patients with FXS have autistic-like traits such as tactile defensiveness, poor eye contact, hand flapping, hand biting, and speech perseveration (Bailey et al., 1998; Baumgardner, Reiss, Freund, & Abrams, 1995; Kerby & Dawson, 1994). Strikingly, about 25–47% of individuals with FXS actually meet the diagnosis for ASD (Bailey et al., 1998; Demark, Feldman & Holden, 2003; Rogers, Wehner, & Hagerman, 2001). Moreover, FXS has been identified as the most common known genetic cause of ASD, with between 1 and 2% of individuals with ASD having the full FXS mutation (Devlin & Scherer, 2012).

A similar situation obtains for ADHD. Some 74% of individuals with FXS meet the criteria for an ADHD diagnosis (Backes, Genç, Schreck, Doerfleur, Lehmkuhl, & von Gontard, 2000), making ADHD the most common comorbid condition diagnosed alongside FXS (Tranfaglia, 2011). Despite these high risk factors for ASD and ADHD, we have consistently noted in earlier sections that behavioral outcomes across individuals with FXS are highly variable, making the investigation of the factors causing individual differences in these symptoms of both theoretical and clinical importance. What factors are involved in the developmental trajectories in many children with FXS to cause them to present with social and cognitive control problems similar to those experienced by children diagnosed with ASD and ADHD, while at the same time there exist other children with FXS who do not display these particular socio-cognitive problems? One research advantage stems from the fact that both FXS and ASD are diagnosed around the same age and substantially earlier than the diagnosis of ADHD (usually only diagnosed in the early school years), making FXS an ideal model for assessing high risk early in development. Indeed, comorbidity in disorders of known genetic origin can serve as models for understanding other disorders that are diagnosed only on behavioral measures, because the genetic disorders can be diagnosed much earlier in development. This is not unique to FXS, of course. Genetic disorders such as Williams syndrome are also characterized by high risk for ADHD symptoms (Rhodes, Riby, Matthews, & Coghill, 2011) and also receive very early diagnosis, often at or shortly after birth. The same holds for infants with Down syndrome. Given the early, and possibly perinatal diagnoses, neurodevelopmental disorders like FXS, Williams syndrome and Down syndrome can be considered models of high risk for those behaviorally defined disorders. However, given the developmental unfolding and variability of these difficulties within and across syndromes, understanding high risk requires moving away from static snapshots, even of individual differences, to developmental trajectories. Furthermore, systematic longitudinal comparisons across these genetically distinct groups with commonly high risk for those behavioral symptoms could lead us to understand the differing developmental trajectories leading to those symptoms.

Nonetheless, the promise of insights from genetic disorders that, like FXS, are diagnosed early and carry a high risk for ASD or ADHD is not necessarily straightforward.

Comorbidity With ASD

A first set of questions that obviously must be raised are the following: are the comorbid autistic-like traits in FXS really the same as those existing in individuals with idiopathic ASD? Or do they constitute instead the severe end of a continuum of cognitive impairment and behavioral difficulties present in more affected individuals? Separating these two interpretations is not an easy endeavor, yet is clearly critical for the development of behavioral and pharmacological treatments that address the core impairments in ASD, ADHD, and FXS. Several researchers have attempted to address this question using behavioral measures. While some have identified similar profiles of autistic traits in both individuals with FXS and those with idiopathic ASD (Bailey et al., 1998), others argue that behavioral profiles are in fact distinct in the two populations (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010; Kaufmann et al., 2004; McDuffie, Thurman, Hagerman, & Abbeduto, 2014). For example, McDuffie and colleagues (2014) designed a study whereby groups of individuals with idiopathic ASD and individuals with FXS were matched on three different criteria: (1) on chronological age regardless of comorbidity (i.e., some members of the FXS group met and others did not meet the ASD diagnostic criteria); (2) on diagnosis (chronological age matches, taking all

the participants with FXS who had received a comorbid ASD diagnosis); and (3) on severity (chronological age together with severity levels of the ASD diagnosis). The three groups were then compared on the basis of their scores on the ADI-R, a tool commonly used in the diagnosis of ASD, which yields a variety of scores within three categories: reciprocal social interaction, communication, and restricted interests/stereotypical behaviors. Comparing idiopathic ASD and comorbid FXS/ASD, the study identified a number of significant differences in scores, for instance, for social smiling and complex behaviors. However, studies based solely on behavior can be problematic, because they tend to match individuals according to ASD severity, or ASD diagnostic criteria, which themselves are behaviorally defined, and then compare groups based on behaviorally defined ASD symptomatology and measures of adaptive behaviors. The risk of circularity is obvious.

Circularity can be surmounted by opting for a different level of analysis, i.e., neurobiological and molecular variation between FXS and ASD or ADHD, using both human and animal models. Taking again the example of ASD, researchers need to raise the very question of why genetically defined FXS would lead to ASD-like symptoms. Here, the major response stems from research that has found that many of the targets of FMRP are indeed the products of genes that have also been implicated in ASD (Darnell et al., 2011). This has caused scientists to argue that FXS leads to ASD or autistic-like symptoms via downstream mechanisms of FMRP. Recent modeling studies have lent support to this claim by modeling how FMRP targets not only contribute to an ASD outcome, but they do so via a number of distinct etiologies. These include single, rare, highly penetrant disruptions in a subgroup of embryonically expressed FMRP targets, as well as multiple less penetrant disruptions with cumulative effects in a subgroup of FMRP targets up-regulated in adolescence and adulthood (Steinberg & Webber, 2013). Such an explanatory framework suggests that *FMR1* silencing would put individuals with FXS at higher risk for comorbid ASD if accompanied by other downstream hits that are also involved in ASD risk factors. This gives rise to a further question: why does non-idiopathic ASD, which may or may not result from genetic disruption downstream of FMRP, share symptoms with genetically defined FXS? This is where animal models become critical. Indeed, molecular work on mice is beginning to shed light on this issue. Research using a common ASD mouse model, the *Nlgn3* KO mouse, has succeeded in creating the same synaptic phenotype as in FXS (Baudouin et al., 2012). Thus, despite distinct etiologies, FXS and at least one example of genetically defined ASD share a core neurobiological phenotype, opening the doors to explore shared therapeutic intervention studies. Moreover, scientists have argued that the notion of shared genetic and neural mechanisms is actually supported also by behavioral findings. For example, Rogers and collaborators (2001) studied two subgroups of young children with FXS between the ages of 21 and 48 months, one of which performed similarly to children with developmental delay but not ASD, and the other whose performance was similar to a group with idiopathic ASD. To explain the subgroup findings, the authors argue that these differences occur because the FXS mutation represents high risk for all individuals, but it is not determinist; additional mutations are likely to work synergistically with the FXS mutation to result in comorbid ASD. In spite of the demonstration of shared genetic and neural mechanisms, there are numerous other functional and anatomical differences between individuals with FXS and those with idiopathic ASD, which supports a contrasting view, that is, that comorbid ASD in FXS may be distinct from those in nonsyndromic, idiopathic ASD (Hazlett et al., 2009). Further in-depth research is clearly necessary to decide between these competing theories. Although variation in the behavioral profiles of individuals with FXS alone, FXS together with comorbid ASD, and idiopathic ASD obviously complicates the picture, the investigation of the genetic and cellular mechanisms of ASD risk in FXS may yield a better understanding of comorbidity in general as well as of the heterogeneous presentation of symptoms across individuals, ultimately resulting in targeted therapeutic interventions based on biological differences.

Comorbidity With ADHD

Very similar approaches need to be taken to understand the mechanisms responsible for the presence of hyperactivity and inattention mechanisms in ADHD and comorbid FXS/ADHD (Scerif & Baker, in press). Idiopathic ADHD is associated with both functional and structural abnormalities of a distributed right lateralized corticostriatal network implicated in inhibitory control. Interestingly, these atypicalities overlap significantly with those implicated by functional imaging studies of inhibitory control problems in FXS (e.g., Hoeft et al., 2007). Early reports of localized structural abnormalities have since been complemented by large-scale studies of cortical development over time (Shaw et al., 2007). Such longitudinal studies have also pinpointed the differences in prefrontal cortical thickness across patients with ADHD that tend to predict

later clinical outcome (Shaw et al., 2006). Functional abnormalities of these circuits in ADHD have also been clearly established: fMRI studies using classical inhibitory control tasks (e.g., go/no-go task, stop-signal reaction time) yield reduced activation of inferior prefrontal cortex and caudate nucleus compared with healthy age-matched controls (Durston et al., 2003), a finding that mirrors the abnormalities found in FXS (Hoeft et al., 2007). Electrophysiological studies also indicate that children with ADHD differ from controls at multiple time points in the information processing cascade leading to the inhibition of a response or when resolving conflict (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005). Again, very similar findings have emerged from electrophysiological studies of adolescents and adults with FXS (van der Molen et al., 2012).

At the level of neurotransmission, the involvement of striatal circuits in ADHD is strongly supported by the fact that methylphenidate (MPH), a dopamine reuptake inhibitor, alleviates symptoms in the majority of affected cases (Volkow, Wang, Fowler, & Ding, 2005). Interestingly, MPH has been shown also to be the most effective pharmacological intervention for treating ADHD-like symptoms in individuals with FXS (Roberts et al., 2011). Intriguingly, recent findings from genome-wide association studies have considerably changed prevailing views on which key genes might be associated with risk for ADHD (Franke, Neale, & Faraone, 2009). Rather than the expected dopaminergic candidates, it is genes involved in neurodevelopmental networks for neurite outgrowth that seem to be more heavily implicated (Poelmans, Pauls, Buitelaar, & Franke, 2011). This turns out to be consistent with recent evidence from the study of rare copy-number variants in ADHD, suggesting that intrinsic neurotransmitter systems, and more specifically metabotropic glutamatergic pathways, are likely to be involved in ADHD risk (Elia et al., 2012). Importantly, these very pathways overlap with those compromised in FXS, suggesting at least one neural pathway of risk for hyperactivity/inattention that is shared between idiopathic ADHD and FXS.

In summary, the high risk for ADHD- and ASD-like symptoms in FXS has attracted the attention of scientists studying those behaviorally defined neurodevelopmental disorders, because multilevel studies of FXS could contribute to a much earlier understanding of the developmental trajectories in the normal population that lead to compromised outcomes in confirmed diagnoses of ADHD or ASD. The longitudinal assessment of very young children with FXS, before their behavioral problems become consolidated, would be especially helpful in this respect, in that it could lead to the identification of potential modifiable protective factors (e.g., environmental inputs such as parent-child interaction and teaching practices). However, this again puts us squarely in the important debate as to whether ADHD and ASD symptoms in FXS are similar to or different from those in idiopathic cases of ADHD and ASD. We argue that a focus on both overlapping and distinct neural mechanisms may advance this debate, especially if it also takes into account potential differences in developmental timing.

RELATIONSHIPS TO THE PRINCIPLES OF DEVELOPMENTAL PSYCHOPATHOLOGY

Throughout this chapter, we have focused in particular on a specific neurodevelopmental disorder and its comparison with other genetic disorders. However, because of their identified etiology, disorders like FXS, WS, and DS offer inroads into the broader and more general principles of developmental psychopathology as a whole (Cicchetti & Toth, 2009). First, their study is increasingly interdisciplinary, bridging scientists who work at complementary levels of enquiry: from cellular neuroscience to systems neuroscience, developmental and cognitive psychology, as well as clinical implementation (e.g., see Fung, Quintin, Haas, & Reiss, 2012, for a review of mechanistic comparisons between FXS and WS). Second, work on specific genetic disorders and their comparison identifies new challenges for developmental cognitive neuroscientists working with neurotypical individuals: if they play such an important role in shaping atypical development (e.g., Karmiloff-Smith et al., 2012), how do typical low-level mechanisms such as attentional biases impact memory and learning trajectories over developmental time (see Scerif & Wu, 2014, for emerging implications in the field of typical attention research)? Third, because the early genetic diagnosis increasingly precedes the emergence of childhood difficulties and it is clear that not all children with disorders like FXS, WS, and DS develop full-blown ADHD or ASD, may offer insights into pathways to protection and resilience. Fourth, in addition to discovering multilevel processes leading to maladaptive and adaptive life span outcomes, researchers in this area now have a range of interdisciplinary tools to ameliorate poor outcomes. Although recent efforts have focused on pharmacogenetics (e.g., Jacquemont et al., 2014), there is also growing interest in complementary effective and syndrome-specific psychosocial therapies (Turk, 2011). We turn to these translational implications in a later section.

FUTURE DIRECTIONS: THE IMPORTANCE OF LONGITUDINAL COMPARISONS ACROSS SYNDROMES OF KNOWN GENETIC ORIGIN

Throughout this chapter, we have argued for the importance of taking a syndrome of known genetic origin to gain a deeper understanding of those neurodevelopmental disorders which are currently only defined in terms of patterns of behavioral deficits. Yet, cross-syndrome comparisons amongst genetic syndromes themselves also turn out to be particularly useful. For example, it is frequently the case that individuals with different genetic syndromes end up with the same behavioral scores on a task. Can we take it that the underlying cognitive and/or neural processes are the same? Not necessarily. Indeed, in a series of cross-syndrome comparisons of genetic syndromes including FXS, Down syndrome (DS) and Williams syndrome (WS), we have revealed different cognitive and neural processes even when scores fall within the normal range on standardized tasks such as the Benton or Rivermead face processing tasks (Karmiloff-Smith et al., 2004). Other studies, e.g., examining sensitivity to numerical displays in infants with genetic syndromes such as DS and WS, revealed different trajectories of saccadic eye movements even though total looking time scores were equivalent across the two syndromes (Karmiloff-Smith, 2012). In comparisons of FXS and WS (e.g., Scerif et al., 2004), we demonstrated the existence of different patterns underlying equivalent behavioral scores. Such subtle differences are crucial to inform both theory and intervention, and underline the importance of syndrome-specific treatment schedules. In general, comparisons across syndromes yield subtle impairments that a focus on a single syndrome would not necessarily reveal. Ultimately, future research in developmental psychopathology should target prospective longitudinal designs that directly compare dynamically changing profiles and trajectories across disorders of identified genetic etiology, at all their interacting levels. Detailed prospective work on developmental dynamics at each level will need to be increasingly complemented by interdisciplinary collaborations bringing together clinicians and researchers working on animal models, systems neuroscience, and developmental psychology.

TRANSLATIONAL IMPLICATIONS

Translational research has been defined as "research designed to address how basic behavioral processes inform the diagnosis, prevention, treatment and delivery of services for mental illness and, conversely, how knowledge of mental illness increases our understanding of basic behavioral processes" (National Advisory Mental Health Council, 2000, p. iii). The convergence between basic scientists and clinicians in the area of genetic disorders is still in its infancy. However, we believe that a cross-syndrome developmental cognitive neuroscience approach will be pivotal in devising intervention attempts that are truly syndrome-specific, rather than focused on a collection of individual behavioral symptoms. To take hyperactivity and inattention, until now the most commonly used approach to treat them in the context of FXS has been stimulant-based treatment (Roberts, Miranda, et al., 2011). A similar approach has characterized the treatment of hyperactivity in WS (Rhodes et al., 2011). In contrast, researchers and clinicians alike have been calling for a mechanism- and syndrome-specific approach to treatment, and one that is sensitive to individual and developmental differences within the spectrum of individuals with FXS (Jacquemont et al., 2014; Turk, 2011). We believe that similar translational implications apply to other neurodevelopmental disorders of identified genetic etiology and high risk of behavioral difficulties. If these difficulties continue to be treated as disparate symptoms, rather than the complex outcomes of multilevel developmental dynamics, treatment approaches will not be optimized to the specific needs of individuals with genetic disorders.

CONCLUDING THOUGHTS

In this chapter we have highlighted the importance of both cross-syndrome comparisons and within-syndrome variability. Indeed, despite very high risk, FXS is not of necessity associated with impairment. In fact, some children with the full FXS mutation function quite well. This is true in the case not only of females, who have the additional unaffected X that may act as a protective factor, but also of some males. So, something protects a limited number boys from risk, which is why we believe that the case of young children with a diagnosis of FXS constitutes an interesting more general model in which to assess early predictors of risk and resilience, as well as early predictors of declining or improving neurocognitive trajectories (Hernandez et al., 2009; Rogers, Wehner, & Hagerman, 2001). This is particularly true of comorbidity with ASD- and ADHD-like symptomatology. Other syndromes of known genetic origin (e.g., Williams syndrome) have also been used as models for a more general consideration of neurocognitive disorders (D'Souza et al.,

2014; Farran & Karmiloff-Smith, 2012; see also Scerif & Wu, 2014). Cross-syndrome comparisons can also be rich sources of information at multiple levels of description (Karmiloff-Smith et al., 2012).

Here, we used the example of fragile X syndrome to illustrate a number of broad points that emerge from the study of genetic syndromes. We overviewed what is known about the FXS genotype and phenotype in terms of cellular, neural, cognitive, and behavioral aspects of the syndrome, in particular emphasizing its developmental nature. Critically, we discussed how recent longitudinal data emphasize the need to focus on variability in outcomes for affected individuals, even in the face of a monogenic disorder. As mentioned above, there is indeed no one-to-one mapping between genetic mutation and phenotypic outcome, but rather a complex, time-dependent pathway across developmental time. The findings on FXS highlight the need to understand diverging developmental trajectories, predictors of greater risk, mechanisms of resilience and environmental protective influences. In summary, we argue that, because they present biologically well-dissected information about genetic origin, syndromes like FXS lend themselves particularly well to study of the high risk of impairment for common behaviorally defined disorders, like ADHD and ASD (see Scerif & Baker, in press, for a review of how this approach might inform an understanding of ADHD risk). However, to understand trajectories leading to good or poor outcomes, as well as their overlap or differences across disorders, a developmentally inspired approach is critical and needs to go beyond behavioral outcomes and be underpinned by knowledge of the developmental cognitive neuroscience of each disorder.

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CHAPTER 3

Autism Spectrum Disorders

RAPHAEL BERNIER and GERALDINE DAWSON

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HISTORICAL CONTEXT

In the early twentieth century Dr. Eugen Bleuler used the term *autism* to describe individuals with schizophrenia who were disconnected from reality ushering in the word into the scientific literature (Bleuler, 1911/1950). Decades later, Dr. Leo Kanner used the term to describe 11 individuals with a pattern of behaviors involving social withdrawal that he felt was distinct from schizophrenia (Kanner, 1943). He referred to this group of patients with challenges in the social and language domains and repetitive behaviors as having early infantile autism. He reported that the patients demonstrated an inability to relate to others as well as social communication challenges including language delays, echolalia, pronominal reversals, and concrete language use. Additionally he described elaborate rituals and routines reflecting a significant insistence for sameness (Kanner, 1943).

During the same time period, Dr. Hans Asperger, working in Europe, described a group of boys with similar challenges in social communication (Asperger, 1944/1991). He described a pattern of difficulties in social interaction including impaired use of eye contact, affective expression, and conversational abilities, similar to Kanner's report. However, in contrast to Kanner's patients, the patients Asperger described had well developed language abilities and often spoke pedantically like adults (Asperger, 1944/1991). Although their vocabulary and grammatical skills were intact, these children had significant impairments in conversational skills and had an unusual use of the volume, tone, and rhythm of speech. Finally, Asperger commented on their tendency to become excessively

preoccupied with singular topics of interest, referring to them as little professors because of their tendency to discuss these interests in great detail.

Early theories on the etiology of autism were based on the prevailing atmosphere of psychological understanding of the middle of the twentieth century. At the time psychoanalytic theory was the prominent perspective on the development of mental illness, and although there are many schools of thought within the field, in general, psychoanalytic theory is based on the notion that mental illness arises from unconscious conflicts resulting from early childhood experiences—most often experiences with parental relationships. As such, based on this perspective, if unconscious conflicts resulting from early development are believed to be the root cause of a childhood disorder and if parents, particularly mothers, are the key component of a child's early development, then parents could be considered the causal factor in the development of disorders for which no clear etiology has been identified. Such was the case with autism.

Following his contemporary theorists, Bettelheim (Bettelheim, 1967) proposed that children with autism withdrew from social interaction and turned inward in response to cold, aloof parents—particularly mothers. However, empirical work in the 1970s and 1980s provided evidence counter to this refrigerator mother theory. Parents of children with autism demonstrated personality measures within the normal range and reported similar levels of marital satisfaction and family cohesion relative to parents of children without disabilities (Koegel, Schreibman, O'Neill, & Burke, 1983; McAdoo & DeMyer, 1978). Early scientific leaders arguing against the refrigerator mother theory proposed that the disorder was due to a neurological impairment (Rimland, 1964) and had a strong genetic component (Folstein & Rutter, 1977), and also proposed that involving parents as part of the treatment was more appropriate and beneficial than treating the parents (Schopler & Reichler, 1971).

In the years since Kanner first reported on 11 children who had an "inability to relate themselves in the ordinary way to people and situations from the beginning of life" (Kanner, 1943, p. 242), there have been tremendous gains in our understanding of the core impairments, etiology, and intervention of autism spectrum disorder.

CORE CHARACTERISTICS

The saying "if you've met one child with autism, you've met one child with autism" speaks to the significant variability in presentation of autism. While each individual with autism presents with a unique constellation of symptoms and corresponding challenges, there are several characteristics that fall within the domains of social communication and repetitive and restrictive behavior and define the ASD diagnosis.

Social Attention

From the first days of life typical infants show preferential attention to their social world, attending to faces, voices, and body movements from very early in life. In contrast, young children with autism pay less attention to people and their actions and movements, instead directing their attention to nonsocial objects (Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011). A primary feature of ASD that emerges by 12 months of age is impaired eye contact (Werner, Dawson, Osterling, & Dinno, 2000; Zwaigenbaum et al., 2005). Toddlers (between the ages of 14 and 42 months of age) with ASD prefer geometric images to images of other children (Pierce, Conant, Hazin, Stoner, & Desmond, 2011), and as opposed to toddlers with either typical development or developmental delays, toddlers with ASD do not show any difficulty disengaging from looking at a face when presented with another stimulus (Chawarska, Volkmar, & Klin, 2010). Two-year-old children with ASD orient to nonsocial contingencies as opposed to biological motion (Klin, Lin, Gorrindo, Ramsay, & Jones, 2009), and preschool-age children with ASD do not show normal preferences for speech sounds (Klin, 1991, 1992; Kuhl, Coffey-Corina, Padden, & Dawson, 2005). Similarly, Ruffman, Garnham, and Rideout (2001) observed intact anticipatory looking during a story task involving nonsocial objects but decreased looking during a story involving human characters in children with ASD compared to children with learning disabilities. This reduced social attention and the observed failure to orient to social stimuli has been termed a *social orienting impairment* and has been noted in preschool-age children with autism and in children as young as 10 months old who go on to develop autism (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Werner et al., 2000). In early work in this area, Osterling and Dawson (1994) viewed videotapes of first birthday parties for children who later went on to develop autism and typically developing children and observed that 1-year-olds with autism oriented less often to social stimuli (faces, speech sounds) in their natural environments. In an experimental effort to characterize social attention abilities in ASD, Dawson et al. (Dawson, Meltzoff, Osterling, Rinaldi, et al., 1998) compared rates of orienting to social stimuli (name calling, clapping) and

nonsocial stimuli (rattle, jack-in-the-box) in children with ASD, and receptive language mental age matched children with Down syndrome and typical development. They found that children with ASD more frequently failed to orient to both types of stimuli but this failure was more pronounced for the social stimuli. This body of literature highlighting deficits in social attention suggests that children with ASD may have reduced sensitivity to reward value of social stimuli. As such, these deficits early in development could subsequently result in other, broad downstream social impairments as the child would have reduced opportunities for social learning as a result of the decreased attention and resources devoted to the social world. Indeed, as described later, disruptions to brain circuitry related to reward mechanisms, such as the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), have been noted in imaging studies of individuals with ASD indicating differences in neurological functioning of reward related neural networks (Dichter et al., 2010; Haznedar et al., 2000; Schmitz et al., 2008; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010).

Joint Attention

Joint attention is defined as the ability to "coordinate attention between interactive social partners with respect to objects or events to share an awareness of the objects or events" (Mundy, Sigman, Ungerer, & Sherman, 1986, pp. 657). By about 9 months of age, typically developing infants begin to look between an object and caregiver and learn to share attention (Walden & Ogan, 1988). This is followed by the incorporation of gesture. By about 12 months of age, infants learn to direct another's attention to an object of interest through gestures such as pointing and also learn to follow another's point (Hannan, 1987). These early emerging joint attention skills are a critical step in the development of spoken language (Bruner, 1975).

Systematic study of joint attention abilities in ASD reveals marked impairments in initiating joint attention, but less so for initiating requests and responding to others' joint attention bids. Children with ASD show less spontaneous sharing or directing of others' attention to an object or action of interest, but less impaired abilities to follow others' gaze and gestures to jointly attend to a point of reference (Mundy, Sigman, & Kasari, 1994; Mundy et al., 1986). Impairments in joint attention, assessed through medical screening visits at 12 and 18 months of age, are present in children later diagnosed with ASD (Baron-Cohen et al., 1996). These joint attention impairments remain consistent over development (Mundy, Sigman, & Kasari, 1990), are linked with later language abilities (Mundy et al., 1990), and are predictive of subsequent diagnosis and degree of social impairment (Mundy et al., 1994; Sigman et al., 1999; Yoder, Stone, Walden, & Malesa, 2009). Given the prominence of these impairments, a deficit in joint attention is considered a core social impairment in ASD (Charman, 2003; Dawson, Toth, et al., 2004; Loveland & Landry, 1986; Mundy et al., 1986; Sigman et al., 1999; Wetherby & Prutting, 1984). Indeed, joint attention deficits correctly classify 94% of children with ASD in relation to children with intellectual disability (Mundy et al., 1986). Considered in a developmental context, the role of joint attention ability is critical to social and language learning. Indeed, the deficits in this social cognitive ability observed in ASD, as demonstrated in the research literature, predict further downstream impairments later in development.

Face Perception

At birth infants show a preference for face-like stimuli (Goren, Sarty, & Wu, 1975), and within the first few days of life typical infants are able to recognize their mother's faces (Bushnell, Sai, & Mullin, 1989). Individuals with ASD have consistently shown impairments in face processing abilities. A failure to look at others was the single best discriminator between 12-month-old infants who were subsequently diagnosed with ASD and those going on to develop typically (Osterling & Dawson, 1994), and as such this lack of attention to faces may be one of the most reliable early indicators of ASD risk (Dawson, Webb, & McPartland, 2005). By middle childhood, children with ASD perform worse than mental-age and chronological-age matched peers on tasks of face recognition (Boucher & Lewis, 1992; Boucher, Lewis, & Collis, 1998; Gepner, deGelder, & deSchonen, 1996) and face discrimination (Tantam, Monaghan, Nicholson, & Stirling, 1989). In a controlled study of face processing in ASD, Klin and colleagues (1999) observed impaired face recognition that could not be accounted for by cognitive delays or impairments in spatial memory. In contrast to typical children, children with ASD are better at recognizing isolated facial features and partially obscured faces (Hobson, Ouston, & Lee, 1988; Tantam et al., 1989) show better face memory performance when focusing on the lower half of the face (Langdell, 1978), but show less attention to the core features of the face such as the eyes and nose (Chawarska & Shic, 2009; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey et al., 2002; Trepagnier, Sebrechts, & Peterson, 2002).

This reduced attention to faces may be the downstream effect of reduced social motivation (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Dawson, Webb, & McPartland, 2005; Klin et al., 1999). Dawson and colleagues proposed that reduced social motivation results in decreased attention to faces that subsequently results in a failure to develop expertise in the perception of faces. Without this experience expectant environment, the brain systems needed to process faces in a typical pattern do not develop (Dawson, Webb, & McPartland, 2005).

Indeed, several studies indicate atypical neural functioning in face perception in ASD. Young children with ASD show an atypical faster neural response using neurophysiological assessment to objects than to faces as opposed to the opposite pattern observed in typical children (Webb, Dawson, Bernier, & Panagiotides, 2006). Preschool-age children with ASD show neural responses to familiar and unfamiliar faces similar to typically developing toddlers, suggesting delayed development in face processing circuitry (Webb et al., 2011). Slower neural responses to faces have been observed in adolescents and adults with ASD (McPartland, Dawson, Webb, Panagiotides, & Carver, 2004; O'Connor, Hamm, & Kirk, 2007), parents of children with ASD (Dawson, Webb, Wijsman, et al., 2005), and 10-month-old infants at risk for ASD (McCleery, Akshoomoff, Dobkins, & Carver, 2009), suggesting that the neural systems underlying face processing may be less efficient and lack specificity to faces. However, not all results have been consistent (for a review, see Dawson, Webb, & McPartland, 2005).

Emotion Perception

By 6 months of age typical infants differentially respond to the emotional displays of those in their environment (Trevarthen, 1979). That is, they smile more and direct more attention to happy faces relative to neutral or sad expressions (Rochat & Striano, 1999; Tronick, Als, Adamson, Wise, & Brazelton, 1978). By the time infants are between 9 and 12 months of age they have learned to utilize others' facial expressions to guide their own behavior when in unfamiliar situations or presented with novel stimuli (Feinman, 1982; Moore & Corkum, 1994). The ability to empathically respond to another's distress also begins to emerge within the first years of life, and is reflected by demonstrations of concern, sharing, helping, and comforting (Rheingold, Hay, & West, 1976; Zahnwaxler & Radkeyarrow, 1990).

In his initial report in 1943, Kanner noted that individuals with ASD are impaired in the recognition of affective cues. A number of empirical studies have demonstrated this observation through carefully controlled experimentation. Studies have shown that children with ASD fail to attend to others' affective displays normally (Bacon, Fein, Morris, Waterhouse, & Allen, 1998; Blair, 1999; Charman et al., 1998; Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Hall, Szechtman, & Nahmias, 2003; Sigman, Kasari, Kwon, & Yirmiya, 1992) and show deficits in recognizing emotional expressions (Bormannkischkel, Vilsmeier, & Baude, 1995; Braverman, Fein, Lucci, & Waterhouse, 1989; Hobson, 1986a, 1986b; Macdonald et al., 1989). Pioneering work in which a familiar examiner pretended to hurt himself or herself by hitting one finger with a plastic hammer and then displayed facial and vocal expressions of distress without using words demonstrated differential response to distress. Sigman and colleagues (1992) observed the behavioral responses of 3- to 4-year-old children with ASD, intellectual disability, and typical development and found that children with ASD often failed to notice or ignored the examiner's affective displays, while the comparison groups were very attentive to the examiner's affective display regardless of the type of emotion displayed. However, employing a similar design, Dawson and colleagues (1998) found that although still attending less than controls, the children with ASD were able to distinguish between emotions; they were more likely to observe and attend to distress relative to a neutral expression. This reduced attention to emotional expressions has also been noted in children with ASD as young as 2 years old (Charman et al., 1998).

The behaviorally observed differences in emotion perception are reflected in observed neurophysiological differences as well. Dawson and colleagues (Dawson, Webb, Carver, Panagiotides, & McPartland, 2004) assessed neural responses to images of a fear face and a neutral face in 3–4-year-old children with ASD as well as typically developing, age matched peers, and chronological and mental aged matched children with developmental delay using event related potentials. During passive viewing of facial expressions the toddlers with ASD failed to demonstrate the increased amplitude to the fear face that was observed in the typical children. Importantly, delays in neural processing of the fear face were associated with reduced social attention assessed through experiments conducted on a different day. Specifically, greater delays in processing the emotional expressions were associated with decreased attention to an experimenter expressing distress, fewer joint attention bids, and reduced social orienting. Importantly, these affective processing delays were not correlated with task performance involving attention to

nonsocial stimuli, such as orienting to nonsocial sounds. This study suggests that children with ASD show deficits in basic aspects of emotion perception by at least 3 years of age and that these challenges are associated with poor social abilities more broadly.

Imitation

Imitation is an early emerging social ability. Newborns as young as 42 minutes old can imitate facial expressions (Meltzoff & Moore, 1977, 1979, 1983) and from there, these early skills develop rapidly over the first years of life with the imitation of actions on objects and imitation of simple gestures, such as waving, emerging around one year of age. Imitation skills progress from simple and familiar actions to increasingly complex, novel, and sequenced behaviors (Meltzoff & Moore, 1994; Piaget, 1962) with the application of imitative actions in novel contexts, emerging between the first and second year, although some researchers suggest the skill emerges earlier (see Bauer, 1996, for review).

It has been proposed that imitation serves as a foundation for social reciprocity and connectedness with others as well as the child's ability to differentiate self from others (Eckerman, Davis, & Didow, 1989; Meltzoff & Gopnick, 1993; Nadel, Guerini, Peze, & Rivet, 1999; Trevarthen, Kokkinaki, & Fiamenghi, 1999; Uzgiris, 1981), developing symbolic play (Piaget, 1962), peer relationships (Trevarthen et al., 1999), language (Avikainen, Wohlschlager, Liuhanen, Hanninen, & Hari, 2003; Charman et al., 2003), and emotional sharing (Hatfield, Cacioppo, & Rapson, 1994). It has also been proposed to play a role in understanding about other's intentions and goals (Kugiumutzakis, 1999; Uzgiris, 1999). In showing that 18-month-old children can imitate others' intended but not completed actions, Meltzoff (1995) proposed that imitation allows a child to understand others' internal states and through the process of learning that the child can produce the same action sequence as what he or she has just observed is a precursor for the development of a theory of mind (Meltzoff & Gopnick, 1993; Rogers & Pennington, 1991).

DeMeyer and colleagues (1972) first reported imitation deficits in ASD after studying nine children with ASD and 12 age-matched children with intellectual disability. The individuals with ASD performed significantly poorer on a large battery of tasks assessing imitation of body movements and actions on objects. The children did not differ in their ability to perform non-imitated actions on objects, suggesting it was imitation and not motor deficits accounting for the observed differences.

Despite the varied testing methodologies, sample characteristics, and comparison groups employed in the studies conducted in the years since DeMeyer and colleagues' report, imitation impairments in ASD have consistently been noted (Williams, Whiten, Suddendorf, & Perrett, 2001). Impairments in the ability to imitate the others' movements, including simple body movements and actions with objects have been observed in young children with ASD (Curcio, 1978; Dawson & Adams, 1984; Dawson, Meltzoff, Osterling, & Rinaldi, 1998; DeMeyer et al., 1972; Sigman & Ungerer, 1984; Stone, Ousley, & Littleford, 1997). Deficits in both immediate and deferred imitation have been noted (Dawson, Meltzoff, Osterling, & Rinaldi, 1998) as well in both *procedural* imitation (i.e., the imitation of actions on novel objects) and *gestural* imitation (i.e., the imitation of meaningless gestures), although gestural impairments were much greater for the autism group (Roeyers, Van Oost, & Bothuyne, 1998). Hobson and Lee found no differences between teens with ASD and age matched peers with intellectual disability in imitation of goal directed actions. However, fewer adolescents with ASD accurately imitated the style with which the experimenter performed the observed action than the control group. They concluded that imitation impairments in ASD reflect a deficit in "the coordination of the representation between the self and other" (Hobson & Lee, 1999). Using a manualized coding system, Bernier and colleagues (Bernier, Dawson, Webb, & Murias, 2007) enlisted trained raters naïve to subject diagnosis to code imitation ability across single step and sequenced behavioral movements in adults with ASD and normal cognitive ability. The adults performed worse on imitative tasks and made more errors in completing the imitative tasks relative to typical peers suggesting imitative deficits are not simply the result of delays in development.

Although there is a general consensus that imitation ability is impaired in ASD, the underlying etiology of particular deficit is still under debate. Theories have attributed imitation impairments to motor praxis impairments and to planning, sequencing, and executing intentional motor movements, although individuals with motor deficits perform better on imitative tasks than ASD (Green et al., 2002; Rogers, 1998). Others have proposed that difficulties in understanding the intersubjective experience of others leads to impairments in matching the movements of self and others (Hobson & Lee, 1999; Meltzoff & Gopnick, 1993). Another theory suggests inadequate procedural learning and inefficient cerebellar-basal ganglia-parietal circuitry contribute to the imitation impairments (Mahone et al., 2006; Mostofsky, Goldberg, Landa, & Denckla,

2000) while neurophysiological and brain imaging studies suggest that a dysfunctional mirror neuron system may play a critical role in imitation deficits (Bernier, Aaronson, & McPartland, 2013; Bernier et al., 2007; Dapretto et al., 2006; Iacoboni & Mazziotta, 2007; Martineau, Cochin, Magne, & Barthelemy, 2008; Oberman et al., 2005; Oberman, Ramachandran, & Pineda, 2008; Rizzolatti & Craighero, 2004; Williams et al., 2006). Regardless of the etiology of the imitation impairments in ASD, given the prominent role of imitative ability to subsequent social cognitive abilities, it is clear that early disruption to imitation can result in deviations from the normal social cognitive developmental tract and result in further downstream developmental challenges for children with ASD.

Symbolic Play

Symbolic representation through pretend play is an important precursor to language development that gradually emerges in the second year of life (Riguet, Taylor, Benaroya, & Klein, 1981; Ungerer & Sigman, 1984). By approximately 20 months of age most children can engage in play in which they attribute animate characteristics to inanimate objects (e.g., pretending that a doll can talk) and can use one object as if it were another (e.g., pretending that a block is a car).

Early reports indicate impairments in symbolic play in ASD. Wulff (1985) stated "the autistic child's play is striking in its lack of fantasy or all other aspects of symbolic play" (pp. 146). Indeed, a key indicator for children who went on to develop ASD noted through a prospective medical screening study was the absence of pretend play at 18 months of age in (Baron-Cohen et al., 1996). Importantly, as their language develops, individuals with ASD show increases in their symbolic play (Amato, Barrow, & Domingo, 1999), and targeted interventions focusing on improving symbolic play yield promising results (Kasari, Freeman, & Paparella, 2006). In scaffolded situations children with ASD can engage in symbolic play (McDonough, Stahmer, Schreibman, & Thompson, 1997), but spontaneous symbolic play is limited, mechanical and repetitive (Wing & Gould, 1978), more akin to learned routines than elaborate, complex, pretend stories (Williams, Reddy, & Costall, 2001). It is unclear if the deficits in symbolic play are the result of a metarepresentational impairment in attending, understanding, and imitating others' actions on objects, that is, a function of joint attention impairments or a function of a generalized cognitive deficit in symbolic thinking, along the lines of an executive function deficit (see (T. Charman, 1997), for a review). Regardless of the cause of the symbolic play deficits, the child with ASD who lacks the opportunity for language and representational learning practiced through play will miss out on the needed opportunities for learning in this arena, resulting in challenges that will only compound with development.

Language and Communication

Given the deficits in the above mentioned early-emerging social communication abilities that are precursors to language development (e.g., joint attention), it is not surprising that many children with ASD have significantly language delays and atypical language development. In fact, language delay is often cited as the initial concern for many parents whose children are later diagnosed with ASD (Chawarska et al., 2007; De Giacomo & Fombonne, 1998; Siklos & Kerns, 2007).

Although it has been historically reported that approximately 50% of individuals with ASD remain nonverbal throughout their lives (Rutter, 1978), this estimate has decreased considerably with advances in earlier diagnosis and intervention. Anderson and colleagues (2007) assessed 9-year-old children with ASD and found that approximately 25% of the children were effectively nonverbal, and another 25% were fluent speakers using complex sentence structure. Findings from longitudinal studies suggest that variability in language ability increases over time, possibly due to responses to intervention (Charman et al., 2005).

Pioneering work in early social communication found that those children with ASD who developed gestural, nonverbal joint attention skills were more likely to develop language (Mundy et al., 1990; Sigman et al., 1999) and a prospective study following high-risk infants who later went on to develop ASD fewer joint attention and gestural behaviors indicating that these early social communicative abilities may be key behavioral indicators of ASD and later language ability (Landa, Holman, & Garrett-Mayer, 2007).

The presence of atypical language is often noted in individuals ASD and limited language. Many individuals with ASD have atypical language characterized by immediate or delayed echolalia (e.g., verbatim repetition of previously heard words or phrases; Rydell & Mirenda, 1994), atypical prosody (e.g., abnormal rhythm, stress, intonation, and loudness; Peppe, McCann, Gibbon, O'Hare, & Rutherford, 2007), neologisms or idiosyncratic language (e.g. the use of made of words; Volden & Lord, 1991), and pronominal reversal (e.g., use of "you" instead of "I" when referring to the self; Cantwell, Baker, Rutter, & Mawhood, 1989; Kanner, 1943).

Despite the presence of language delays and atypical use of language, the most pronounced language impairments in ASD fall in the pragmatic, or social, aspects of language use (see Tager-Flusberg, 1999, 2001, for reviews). Noted characteristics of conversational exchanges with individuals with ASD include the use of irrelevant detail in conversations (e.g., providing dates and ages when discussing a particular event or person), perseveration of particular topics, pedantic speaking on a particular topic of conversation, inappropriate shifts to a new topic without context or consideration of the listener, and a lack of responsiveness to conversational topic initiations introduced by another person (Eales, 1993; Paul, Orlovski, Marcinko, & Volkmar, 2009; Tager-Flusberg, 1999, 2001). These challenges, along with reduced responses to questions and fewer spontaneous offerings of information disrupt the sense of reciprocity in conversational exchanges (Capps, Kehres, & Sigman, 1998). These difficulties with the social aspect of language are also observed among highly verbal adults with ASD (Lord & Paul, 1997). It has been proposed that these pragmatic deficits are the result of impairments in understanding another's intention during conversations (Eales, 1993) or because individuals with ASD have difficulty taking the listener's perspective into account (Tager-Flusberg, 1993, 1996). This difficulty is reflected in atypical language use such as abnormal pronoun use (e.g., saying "You want a drink" when meaning "I want a drink") and inaccurate application of questions and statements (e.g., saying "Want milk?" instead of stating "I want milk").

Language comprehension difficulties have been noted in ASD as well. Many individuals have difficulty understanding non-literal language such as irony, sarcasm, and metaphor (Happe, 1995; MacKay & Shaw, 2004; Martin & McDonald, 2004). Studies also suggest that individuals with ASD also struggle to understand vocal utterances based on stress patterns (Peppe et al., 2007) or identify affective content in a voice (Korpilahti et al., 2007; Rutherford, Baron-Cohen, & Wheelwright, 2002). Rapin (1996) noted that many individuals with ASD seem to have greater challenges in understanding other people's language than they do in learning the specific language structures necessary to produce language (Rapin, 1996). For example, in a study of children with ASD compared to children with specific language impairment, the children with ASD tended to rely on a syntactically based word order strategy rather than relying on the semantic content to determine the meaning of a sentence (Rhea Paul, Fischer, & Cohen, 1988).

It is becoming clear that the language delays and atypical language observed in ASD often result from and interact with other deficits such as comorbid language processing deficits (Bishop & Norbury, 2002; Rapin & Dunn, 2003; Tager-Flusberg, 2004); difficulties in theory of mind (Paul et al., 2009; Tager-Flusberg, 2000); and repetitive behavior being reflected in stereotypical speech patterns (Bodfish, Symons, Parker, & Lewis, 2000; Gabriels, Cuccaro, Hill, Ivers, & Goldson, 2005).

Restricted and Repetitive Interests and Behaviors

Restricted and repetitive interests and behaviors (RRBs) are considered a core diagnostic feature of ASD (Lord & Luyster, 2006; Lord et al., 2006) and were identified as part of Kanner's initial report on ASD. RRBs include repetitive, stereotypic motor mannerisms such as hand flapping, finger flicking, or complicated whole body movements such as posturing or spinning and repetitive use of objects, such as lining things, spinning the wheels of a toy car, playing with strings, repeatedly dropping something from the same height. RRBs also include interests that are unusual in their focus, such as an interest in street signs or toilets, or in their intensity, such as a focused preoccupation on a particular topic typically involving the memorization of facts (e.g., train timetables). An insistence on sameness, reflected in difficulties with transitions or changes to routines or by the presence of ritualized sequences of actions or the precise arrangement of space also falls under the category of RRBs. Finally, sensory interests, such as interests in the sight, sound, smell of things or people (e.g., interest in hair) and aversions (e.g., aversions to specific sounds or particular textures, sound sensitivities necessitating removal from stimuli or situation) are also components of this category.

The observed sensory related challenges can be subdivided to reflect sensory over-responsivity (e.g., negative responses to specific sensory stimuli such as lights or sounds), sensory underresponsivity (e.g., reduce responsiveness to various sensory stimuli), and sensory seeking (e.g., actions performed to increase sensation) (Dunn, 1997; Miller, Anzalone, Lane, Cermak, & Osten, 2007). All three of these sensory processing profiles have been observed in individuals with ASD (Baranek, David, Poe, Stone, & Watson, 2006). Rates of sensory overresponsivity in ASD range from 56 to 70% (Baranek et al., 2006; Ben-Sasson et al., 2007) with common manifestations including distractibility because of the noise emitted by fluorescent lights or a distant siren. However, the same

children with overresponsivity can at times show underresponsivity such as in the form of insensitivity to pain. It has been suggested that impaired ability to modulate sensory information underlies these challenges observed in ASD (Ornitz, 1989).

It has been proposed that RRBs in ASD fall in two distinct categories: lower level behaviors including repetitive motor movements and higher level behaviors that are characterized by insistence on sameness and circumscribed interests (Turner, 1999). The lower level behaviors appear to occur more often in younger children with ASD or children with comorbid intellectual impairments (Wing, 1988; Wing & Gould, 1979), while the higher level behaviors are observed in children without significant intellectual impairments. Both forms of RRBs appear by 2 to 3 years of age (Bishop, Richler, & Lord, 2006; Honey, McConachie, Randle, Shearer, & Le Couteur, 2008; Militerni, Bravaccio, Falco, Fico, & Palermo, 2002; Mooney, Gray, & Tonge, 2006) and longitudinal studies suggest that they persist into adolescence and adulthood (Piven, Harper, Palmer, & Arndt, 1996; Rumsey, Rapoport, & Sceery, 1985).

No specific type of repetitive behavior is specific to ASD as RRBs are observed in typically developing infants and young children (e.g., Evans et al., 1997; Thelen, 1979), and in other neurodevelopmental and psychiatric disorders (Frith & Done, 1990). For example preferences for routines and distress from changes to expectations are observed in typically developing young children (Evans et al., 1997) and in individuals with psychiatric disorders, such as obsessive-compulsive disorder, and repetitive mannerisms are often seen in individuals with intellectual disability. However, relative to typical development in which these behaviors happen fleetingly and to other disorders, in ASD these behaviors occur more frequently (Matson, Dempsey, & Fodstad, 2009). Indeed, the observed pattern of multiple types and severity of RRBs can aid in the discrimination of ASD from other disorders (Bartak & Rutter, 1976; Bodfish et al., 2000; Charman & Swettenham, 2001).

More research is needed to elucidate the relationship between RRBs and the social communication impairments characterizing ASD. Historically, studies examining early emerging ASD characteristics suggested that social communication impairments were the first indicators to emerge in ASD (Baron-Cohen et al., 1996; Cox et al., 1999; Osterling & Dawson, 1994; Robins, Fein, Barton, & Green, 2001); however, recent prospective studies of at risk infant siblings of children with ASD suggest that RRBs, including spinning and spending more time attending to objects observed at 12 months of age are predictive of subsequent ASD symptoms and diagnosis (Ozonoff, Heung, Byrd, Hansen, & Hertz-Picciotto, 2008; Zwaigenbaum et al., 2005). While some argue for an underlying continuous factor of ASD symptoms rather than distinct domains of impairment (Constantino et al., 2004), others cite twin studies showing that these ASD domains are only modestly correlated and conclude they are likely distinct (Happe, Ronald, & Plomin, 2006). The presence of circumscribed interests may provide insight. These intense, perseverative interests usually involve memorization of facts about a specific topic (e.g., cameras, trains) that are nonsocial in nature (South, Ozonoff, & McMahon, 2005) and appear to be common to ASD (one study found that approximately 88% of children with ASD had circumscribed interests) regardless of intellectual functioning or symptom severity (Lam, Bodfish, & Piven, 2008). The nonsocial focus of these interests could diminish motivation and opportunities for social experiences, such that decreased reward salience for social stimuli and increased valence for non-social stimuli could result in the sequelae of impairments observed across both domains in ASD.

DIAGNOSIS AND ASSESSMENT OF ASD

There is currently no biological marker or medical test for making a diagnosis of ASD. The diagnosis is made through careful evaluation of developmental history and caregiver report of symptomatology and observation of the presence (or absence) of behaviors across the two domains of ASD: social communication and repetitive and restricted behavior. The two widely used systems for diagnosing ASD include the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. (*DSM-5*; American Psychiatric Association, 2013) and the *International Classification of Diseases,* 10th ed. (*ICD-10*; World Health Organization, 1992). The specific criteria are described in Table 3.1.

Changes in the Diagnosis

The *DSM-5* was revised in 2013 following nearly two decades of research into ASD (American Psychiatric Association, 2013). With the revised *DSM*, the previous diagnostic umbrella term *pervasive developmental disorders* is no longer used, and the three diagnostic subtypes of autistic disorder, Asperger's disorder, and pervasive developmental disorder–not otherwise specified are collapsed into one term: autism spectrum disorder. Although controversial, the *DSM* committee's decision to collapse all three diagnostic subtypes under one diagnosis was

TABLE 3.1 ***DSM-5*** **Diagnostic Criteria for Autism Spectrum Disorder**

(A) Clinically significant, persistent deficits in social communication and interactions across multiple settings, currently or by history, as manifested by all of the following:
  1. Deficits in social-emotional reciprocity
  2. Marked deficits in nonverbal communication used for social interaction
  3. Failure to develop, maintain, and understand relationships

(B) Restricted, repetitive patterns of behavior, interests, and activities, currently or by history, as manifested by at least two of the following:
  1. Stereotyped or repetitive motor movements, actions on objects, or speech
  2. Insistence on sameness and excessive adherence to routines or ritualized patterns of behavior
  3. Highly restricted, fixated interests
  4. Hyper- or hyporeactivity to sensory input or unusual sensory interests

(C) Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)

(D) Symptoms must cause clinically significant impairment in social, occupational, or other areas of functioning

based on findings that no specific etiology was tied to the subtypes, no treatment was specific to each subtype, and even experienced clinicians were unable to agree on which children should be diagnosed with each subtype (King, Navot, Bernier, & Webb, 2014; Lord et al., 2011). Other changes included the collapse of three domains of impairment (social, communication, and restricted/repetitive behaviors) into two domains (social communication and restricted/repetitive behaviors). The collapsing of the domains was to reflect that all communication is social in nature and that certain symptoms under the previous system could be counted in both the social domain and the communication domain giving additional weight to a particular symptom (King et al., 2014). Finally, qualifiers, a severity rating system, the inclusion of sensory sensitivities to the RRB domain, and the removal of the requirement that deficits be observed by 3 years of age were all changes made during this revision process.

Domains of Impairment, Qualifiers, and Severity

As shown in Table 3.1, to meet diagnostic criteria for ASD, a child must have deficits in three areas in the social communication domain, at least two of the four possible symptoms in the RRB domain. These impairments may not become evident until the social demands exceed the capacities of the individual and to reflect that there has been a shift from the previous requirement of symptoms present prior to three years of age to an allowance for diagnosis later in life and even adulthood.

With the adoption of the *DSM-5* criteria, qualifiers have been appended to the diagnostic description for an individual. Due to the commonality of the behaviors seen across the *DSM-IV* ASD subtypes, the *DSM-5* committee concluded that the constellation of impairments observed in ASD are best represented as a single yet multidimensional disorder that manifests it uniquely for each individual due to differing cognitive and language abilities, and comorbid disorders (Rutter, 2011). As such, qualifiers to the ASD diagnosis include the presence of co-occurring intellectual or language impairment and association with a known medical or genetic condition or environmental factor. Severity levels have also been incorporated into the *DSM-5* diagnostic process with three levels of support defined for each ASD domain. The levels range from level 1, requiring support, which reflects a severity level such that if a child were without supports, the child's deficits in social communication would cause noticeable impairments spanning level 2, requiring substantial support, and progressing to level 3, requiring very substantial support, which for the social communication domain is defined as deficits in verbal and nonverbal social communication skills that cause severe impairments in functioning (American Psychiatric Association, 2013).

RELATED SYMPTOMS AND COMORBID DISORDERS

Intellectual Disability

Current estimates of the rate of intellectual disability (i.e., IQ below 70) in individuals with ASD are at approximately 40% with higher rates of comorbidity observed in girls with ASD (Baird et al., 2000; Centers for Disease Control and Prevention, 2009, 2012; Chakrabarti & Fombonne, 2001). These estimates differ from earlier estimates published between 1966 and 1999, reviewed by Fombonne (1999), which ranged from 44 to 100% with rates of individuals without intellectual disability estimated at 25.4%, mild to moderate impairment at 23.2%, and severe to profound mental impairment estimated at 55.5%. The decline in the rate of comorbid intellectual disability among individuals with ASD is likely a function of increased diagnostic rates of individuals with intact cognitive abilities along with the effectiveness of early intervention (Chakrabarti & Fombonne, 2005; Fombonne, 2003a, 2003b; Matson & Shoemaker, 2009; Newschaffer, Falb, & Gurney, 2005a).

The diagnostic differential between intellectual disability and ASD lies most clearly in the display of specific impairments in joint attention, motor imitation, symbolic play, theory of mind, and expressive versus receptive language skills (Maljaars, Noens, Scholte, & van Berckelaer-Onnes, 2012; Poon, Watson, Baranek, & Poe, 2012; Wong & Kasari, 2012) observed in ASD. Although some investigators report a specific pattern of intellectual abilities such that individuals with ASD perform better on nonverbal visual–spatial tasks relative to verbal tasks (Fombonne, 2003b; Happe, 1994; Lockyer & Rutter, 1970; Matson & Shoemaker, 2009), others have failed to observe this (Mayes & Calhoun, 2003; Minshew, Turner, & Goldstein, 2005; Siegel, Minshew, & Goldstein, 1996; Szatmari, Tuff, Finlayson, & Bartolucci, 1990), or note that this cognitive profile is not consistent across the age span (Ankenman, Elgin, Sullivan, Vincent, & Bernier, 2014).

Communication Disorders

Given the previously reported deficits in language and communication, communication disorders are often diagnosed at some point in the diagnostic journey for an individual with ASD. Many of the language impairments observed in ASD are reflected in the diagnosis of language disorder, characterized by deficits in comprehension or production of language, although the early emerging social deficits and presence of stereotypic interests or behaviors can readily differentiate language disorder from ASD (American Psychiatric Association, 2013). Speech sound disorders, defined by persistent deficits in speech sound production can also be diagnosed in many children with ASD and may be linked to common underlying etiologies. For example, as described already, many individuals with 16p11.2 deletion have speech sound disorders, but this also one of the most common risk factors for ASD, such that many children with 16p11.2 deletion have both ASD and speech sound disorders (Hanson et al., 2014).

The *DSM-5* also includes a new diagnostic classification related to communication impairment: social communication disorder (SCD). The *DSM-5* defines SCD as persistent difficulty with verbal and nonverbal communication, such as difficulties with spoken and written language and conversational impairments, that is not better accounted for by cognitive impairments. These social communication impairments overlap with many ASD symptoms rendering the differential diagnosis difficult; however, the SCD diagnosis specifies the absence of repetitive or stereotyped behaviors. The lack of repetitive or restricted behaviors differentiates ASD and SCD. As such, ASD must be ruled out before making a diagnosis of SCD.

Attention-Deficit/Hyperactivity Disorder

Prior to the *DSM-5*, attention-deficit/hyperactivity disorder (ADHD) and ASD were considered exclusive of one another and a diagnosis of ASD precluded a diagnosis of ADHD (American Psychiatric Association, 2000). However, some individuals do show symptoms of ADHD, including inattention, hyperactivity, and impulsivity, and the *DSM-5* now allows for the presence of both conditions in one individual (Mayes, Calhoun, Mayes, & Molitoris, 2012). Over the past 10 years, study of the overlap between the two disorders has expanded considerably with a focus on common etiology, similar neurological origins, the evidence for comorbid occurrences, and the implications of a dual diagnosis. Common genetic events have been identified between both disorders (Williams et al., 2010) and decreased prefrontal cortex activation has been reported in both ASD and ADHD (Happé, Booth, Charlton, & Hughes, 2006), providing putative biological bases for the overlap in symptom presentation. Indeed, rates of comorbidity across ASD and ADHD range from 33 to 78% (Gargaro, Rinehart, Bradshaw, Tonge, & Sheppard, 2011; Goldstein & Schwebach, 2004; Sinzig, Walter, & Doepfner, 2009). Interestingly, for those individuals dually diagnosed with ASD and ADHD, oppositional behavior, but not anxiety or ADHD symptom severity is more often reported (Grzadzinski et al., 2011).

Anxiety and Mood Disorders

Co-occurring anxiety and mood disorders are commonly reported in individuals with ASD (Strang et al., 2012; Whitehouse, Durkin, Jaquet, & Ziatas, 2009; Whitehouse, Watt, Line, & Bishop, 2009), however, it is sometimes difficult to identify these symptoms, especially in individuals with ASD who have poor ability to report their internal states. For example, social phobia and social withdrawal may be manifestations of anxiety and depression, respectively, or the result of social impairments related to ASD. Given the clinician's reliance on self-report of symptoms in the assessment of anxiety and mood disturbances and the observation that individuals with ASD often have difficulty identifying and describing their own emotions and feelings (Gillott, Furniss, & Walter, 2001), the ability to detect these symptoms is sometimes challenging. The clinician often must rely on parent or supplemental reports

(Stewart, Barnard, Pearson, Hasan, & O'Brien, 2006), which are known to be less reliable than self-report for both disorders. Further, it is difficult at times to determine if these symptoms are actually distinct diagnoses or rather a characteristic of the disorder (e.g., obsessive compulsive symptoms). Importantly, both anxiety and depression are both responsive to pharmacological and behavioral intervention in individuals with ASD.

Depression in ASD often manifests as an increase in agitation, social withdrawal, and compulsions along with changes in sleep and appetite. Rate estimates for comorbid depression and ASD range from 1 to 58% (Lainhart, 1999; Mayes, Calhoun, Murray, Ahuja, & Smith, 2011). Studies suggest that symptoms of depression are often observed during adolescents in individuals with ASD who have greater insight into their social communication challenges, behavioral differences show an increase in wanting to develop friendships (Kim, Szatmari, Bryson, Streiner, & Wilson, 2000; Mayes et al., 2011).

Research in depression and ASD suggests that even though an individual with ASD may not meet full diagnostic criteria for a comorbid depressive disorder, the manifestation of depressive symptoms can still significantly impact his or her quality of life (Leyfer et al., 2006a; Simonoff et al., 2008). Interestingly, it has been noted that the rate of suicidal ideation is less likely in individuals with ASD and depression such that suicidal ideation is 2.6 times more likely to occur in children with depression alone than in children with both disorders (Mayes et al., 2012; Stewart et al., 2006). A systematic review of several large-scale studies, however, indicated that individuals with ASD comprised 7.3–15% of suicidal populations. This is a substantial subgroup. Several risk factors for suicide among individuals were also reported including peer victimization, behavioral problems, Black or Hispanic ethnicity, lower socioeconomic status, and lower level of education (Segers & Rawana, 2014).

Difficulties with the assessment and characterization of anxiety in ASD have made establishing the prevalence of co-occurrence challenging and as a result study estimates have varied considerably (Leyfer et al., 2006a; Mayes et al., 2012; Simonoff et al., 2008). Studies report ranges from 7 to 84% with the most commonly co-diagnosed disorders being generalized anxiety disorder, agoraphobia, and simple phobia (Gillott et al., 2001; Lainhart, 1999; Leyfer et al., 2006b). Challenges in the symptom overlap make disentangling the disorders difficult. For example, symptoms of obsessive-compulsive disorder (OCD) can resemble the ritualized and repetitive behavior observed in ASD. Although OCD can be differentiated from ASD in that individuals with OCD are more often fixated on a single compulsion than individuals with ASD (Russell, Mataix-Cols, Anson, & Murphy, 2005; Russell & Sofronoff, 2005; Wakabayashi, Baron-Cohen, & Ashwin, 2012), this requires careful clinical investigation. And, similar to depression, certain subgroups of ASD may be more prone to anxiety disorders such that adolescents with intact cognitive abilities may be more likely to have comorbid anxiety than others (Kim et al., 2000; Mattila et al., 2010; Mayes et al., 2011).

Self-Injurious Behaviors

Self-injurious behaviors can include head banging, head slapping, hair pulling, and finger or hand biting and have been observed in individuals with ASD. However, the presence of these behaviors may be more linked to cognitive and language deficits in ASD, rather than ASD itself (Dawson, Matson, & Cherry, 1998). It has been suggested that self-injurious behaviors can be the expression of frustration in individuals with limited communication ability to express feelings or needs (Donnellan, Mirenda, Mesaros, & Fassbender, 1984; Lainhart, 1999). Regardless of the origin, self-injurious behaviors are associated with increased perceived stress in families (Bishop, Richler, Cain, & Lord, 2007); however, behavioral treatments can prove effective in reducing these behaviors.

Seizures

Epilepsy is diagnosed in 6–50% of individuals with ASD depending on the study source with population-based studies reporting lower rates of 5% and epilepsy specific clinics citing rates of 15–30% (Clarke et al., 2005; Matsuo, Maeda, Sasaki, Ishii, & Hamasaki, 2010). Seizure onset most often occurs either early in childhood or in adolescence (Parmeggiani et al., 2010) with early onset seizures associated with poorer outcomes (Saemundsen, Ludvigsson, & Rafnsson, 2008). Given the increased likelihood for seizures in ASD, it is recommended that individuals with ASD suspected of having seizures be promptly evaluated (Filipek et al., 2000).

Gastrointestinal Problems

Gastrointestinal (GI) problems, including constipation, abdominal pain, bloating, diarrhea, and nausea, are estimated to impact between 9 and 70% of children with ASD (Buie et al., 2010). The relationship between GI

impairments and ASD is unclear, but recent work suggests a shared genetic etiology for atypical neuronal development in both the central nervous system, impacting brain development and the enteric nervous system, impacting gut motility, that might lead to comorbid challenge in a subset of children with ASD (Bernier et al., 2014). Another avenue of investigation suggests anxiety may be playing a role. Studies indicate significantly higher rates of anxiety in children with GI problems (Mazurek et al., 2013; Nikolov et al., 2009).

Sleep Problems

Sleep problems are commonly reported in children with ASD with reports indicating that between 44 and 83% of children with ASD have severe sleep problems (Allik, Larsson, & Smedje, 2006a, 2006b; Goldman, Richdale, Clemons, & Malow, 2012; Goldman et al., 2009; Krakowiak, Goodlin-Jones, Hertz-Picciotto, Croen, & Hansen, 2008; Owens, Spirito, McGuinn, & Nobile, 2000; Patzold, Richdale, & Tonge, 1998; Richdale, 1999; Richdale & Prior, 1995). Reported sleep problems include difficulty falling and staying asleep, early-morning waking, and overall shortened sleep times. These problems are most often reported in children under 5 years of age, but sleep problems persist for many despite age related improvements. The cause of sleep disturbances in ASD remains unknown, but disruptions to melatonin synthesis (Richdale, 1999), alterations in melaton regulation (Rapin & Katzman, 1998), disruptions to arousal (Richdale & Prior, 1995), and anxiety (Wagner, 1991) have been proposed as possible etiologies. Regardless of the origin, actigraphy, an objective measure of sleep, indicates that children with ASD sleep shorter amounts than children with typical development or developmental delays (Goodlin-Jones, Tang, Liu, & Anders, 2008). Treatment for sleep disturbances in ASD, including supplemental melatonin, has been shown to be effective through both actigraphy and parent report of sleep and behavior (Doyen et al., 2011; Malow, Adkins, et al., 2012; Malow, Byars, et al., 2012; Rossignol & Frye, 2011). Further, treatment for sleep difficulties appears to also improve related symptoms such social interaction, repetitive behaviors, affective problems, oppositional and aggressive behavior, and inattention/hyperactivity symptoms (Goldman et al., 2009, 2012; Malow, McGrew, Harvey, Henderson, & Stone, 2006). Given the frequent concerns regarding sleep problems in ASD, the effectiveness of treatment, and the associated improvements in other behaviors following sleep treatment, it is important that assessment and management of sleep concerns be a routine part of clinical care for children with ASD.

Regression

While development can progress atypically from very early in life in ASD, symptoms may also appear following a loss of skills previously developed. This regression is estimated to occur between 20% and 47% of children with ASD (Goldberg et al., 2003; Lord, 1995; Rapin & Katzman, 1998; Rutter & Lord, 1987) with typical regression onset between 18 and 24 months of age (Davidovitch, Glick, Holtzman, Tirosh, & Safir, 2000; Fombonne & Chakrabarti, 2001; Kurita, 1985, 1996; Rapin & Katzman, 1998; Rutter & Lord, 1987; Shinnar et al., 2001; Wilson, Djukic, Shinnar, Dharmani, & Rapin, 2003). Some reports suggest that individuals with regression have poorer outcomes (Luyster et al., 2005) while others have found that there are no differences between children with and without regression on language, cognitive, or behavioral outcomes at age 3 to 4 years (Werner & Dawson, 2005). Loss of language skills is most often reported but can include social engagement, cognitive ability, and adaptive skill loss. Any loss of skills warrants immediate evaluation (Filipek et al., 1999).

EARLY IDENTIFICATION

Most parents report concerns with their child with ASD's development by 18 months of age (Howlin & Asgharian, 1999; S. Rogers, 2001), but the mean age of diagnosis across the United States ranges from 38 to 120 months (Daniels & Mandell, 2013) with an average age of 3.1 years (Mandell, Novak, & Zubritsky, 2005). However, the age at which a child receives a diagnosis is decreasing as a result of increased awareness, improved screening techniques, and more expertise; earlier identification is important for intervening earlier and therefore improving outcomes.

Established practice parameters have helped to improved screening of ASD in young children. In 2000, the American Academy of Neurology issued practice parameters outlining a two-tiered screening approach for ASD. The first level focuses on the identification of children at risk for atypical development (followed by identifying those specifically at risk for ASD) through routine developmental surveillance conducted at all well-child visits. The second level entails formal diagnostic procedures conducted by expert evaluators focusing on the diagnosis

TABLE 3.2 Red flags indicating need for further evaluation for ASD

Further developmental evaluation is warranted if a child fails to meet any of the following:
Babbling by 12 months
Gesturing (e.g., pointing, waving bye) by 12 months
Using single words by 16 months
Using spontaneous (not echoed) two-word phrases by 24 months
OR if there is a loss of language or social skills at any age

of ASD (Filipek et al., 2000). Importantly, these parameters stipulated that should a child fail to meet certain milestones or demonstrate a loss of language or social skills at any time, then further evaluation is warranted (Table 3.2). The American Academy of Pediatrics clarified that in addition to routine level 1 surveillance to identify children at risk for developmental delay, specific screening using an autism specific screening tool should be utilized at 18 and 24 months of age regardless of any identified risks (Johnson, Myers, & American Academy of Pediatrics Council on Children With Disabilities, 2007).

Several screening measures for infants at level 1 screening have been developed that meet the American Academy of Pediatrics' recommendations. Some of these include the modified CHAT (M-CHAT), the Pervasive Developmental Disorders Screening Test, and the First Year Inventory and Infant Toddler Checklist. The M-CHAT (Robins et al., 2001) and Pervasive Developmental Disorders Screening Test (Siegel, 2004) are both level 1 questionnaire-based screening instruments designed to quickly capture parent report of their toddlers. The First Year Inventory (Baranek, Watson, Crais, & Reznick, 2003) lowers the age boundary to 12 months for parent report in level 1 screening. The Screening Tool for Autism in Toddlers (Stone, Coonrod, & Ousley, 2000) and the Communication and Symbolic Behavior Scales Developmental Profile (CSBS; Wetherby & Prizant, 2002) are both interactive tools for use in level 2 screening. Through 20-minute, play-based interactions, clinicians can gather information regarding the presence of ASD and generate targets for intervention. The CSBS also includes a general developmental screener, the Infant Toddler Checklist, and a follow-up caregiver questionnaire in addition to the play based interaction.

There is a considerable increase in the ability to diagnose autism at younger ages and research to indicate a diagnosis can be reliably diagnosed by 20 to 24 months of age (Baron-Cohen et al., 1996; Rogers, 2001). Further, studies suggest that early diagnoses remain stable over time such that diagnoses made in the first two years of life are retained by age 3 (Baron-Cohen et al., 1996; Lord, 1995; Stone et al., 1999). These findings underscore the importance of early detection, followed by diagnosis so that intervention can begin as early in development as possible.

EPIDEMIOLOGY

Prevalence

Once thought to be a rare disorder, ASD is now one of the most common developmental disorders. In the 1980s, the prevalence of ASD was estimated to be 4 per 10,000 individuals (Ritvo et al., 1989), but estimates currently suggest more than 1% of children in the United States (1 in 68) are affected (Centers for Disease Control and Prevention, 2014). Multiple studies have reported an increase in prevalence of ASD diagnosis (Cavagnaro, 2009; Centers for Disease Control and Prevention, 2009, 2012; Hertz-Picciotto & Delwiche, 2009; King & Bearman, 2009; Newschaffer, Falb, & Gurney, 2005b) although it remains unclear if the increase in diagnosis is strictly related to improved identification and broadening definitions or if there is a true increase in prevalence (Rice et al., 2012). A meta-analysis spanning 20 studies between 1966 and 1997 revealed that the prevalence rate for children born before 1970 was 4.7 cases per 10,000 while the rate for those born in 1970 or later was 11.2 per 10,000 (Gillberg & Wing, 1999). Similar to the recent CDC studies, this analysis yielded an estimated annual increase in autism diagnoses of 3.8 percent per year, mirroring rising international prevalence rates (Fombonne, 2009). Current research examining the multiple ASD risk factors, including genetic and prenatal and early postnatal environmental factors and their interaction, that contribute to risk for autism may illuminate the cause of the changing diagnostic rates (Newschaffer et al., 2007).

Gender

Males are diagnosed at approximately a 4:1 rate relative to females (Fombonne, 2009). A variety of mechanisms have been proposed, including endogenous hormones (Knickmeyer & Baron-Cohen, 2006; Knickmeyer et al., 2006), intrauterine exposures that impact male but not female growth (Hertz-Picciotto et al., 2006), and X-chromosome inactivation (Nagarajan et al., 2008). More recently it has been demonstrated that females have a higher mutational burden, more deleterious structural mutations in autosomal chromosomes, than males, suggesting increased numbers of genetic events, not linked to variants on the X chromosome, contribute to the development of ASD in females (Jacquemont et al., 2014).

Finally, it has been suggested that the diagnostic tools may be biased toward identifying ASD in males (Rivet & Matson, 2011), which underscores the limited research on the diagnosis of females with ASD (Rutter, Caspi, & Moffitt, 2003).

Sociocultural Influences

Socioeconomic status (SES) and race have both been associated with ASD diagnosis. In European countries supporting population wide surveillance and universal health care, SES does not appear to be a factor in the prevalence of ASD; however studies conducted in the United States indicate an underascertainment of families with low SES backgrounds (Baird et al., 2006; Fombonne, Du Mazaubrun, Cans, & Grandjean, 1997; Larsson et al., 2005). Race is also associated with ASD. Differential prevalence rates of ASD have been observed based on ethnicity with the odds of having an ASD being 57% lower for non-Hispanic, African American children, than non-Hispanic, Caucasian children (Kogan et al., 2009). The age at which a child is diagnosed also varies with ethnicity. One study suggested that on average, Caucasian children are diagnosed 1.5 years earlier than African American children, and $2\frac{1}{2}$ years earlier than Latino children (Mandell, Listerud, Levy, & Pinto-Martin, 2002). The association between SES and ASD is likely due to reduced availability of diagnostic and treatment resources for families with lower SES (Kogan et al., 2009) as opposed to an association with etiology. Similarly, it is likely other factors driving the association between race and ASD. For example, it has been suggested that parents of certain ethnic backgrounds may emphasize disruptive or other behaviors during assessment rather than social oddities, leading to a reduced likelihood of an ASD diagnosis (Mandell et al., 2002). Alternatively, it has been proposed that general prejudices held by the clinician can lead to misguided expectations about the probability of ASD occurring in different ethnicities (Balsa, McGuire, & Meredith, 2005). Ultimately, the existing literature suggests that ASD does not discriminate based on racial or socioeconomic background.

ETIOLOGY

No one clear cause of ASD has been identified, although significant advances have been made toward genetic susceptibility factors and potential environmental triggers. It is generally considered that ASD has a variety of contributors including genetic and environmental factors.

Genetic Risk Factors

Twin Studies

The first clear indication that ASD had a strong genetic component was from Folstein and Rutter's (1977) study of twins with ASD. In their same-sex epidemiological study they found a 36% concordance rate for MZ twins and a 0% rate for DZ twins. Subsequent twin studies have replicated these findings with concordance rates ranging from 60–96% in MZ twins compared to 0–23% in DZ twins (Bailey et al., 1995; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985; Steffenburg et al., 1989). However, a recent California based population study of twins with ASD observed that common environmental factors may contribute approximately 55% of the ASD risk with genetic heritability accounting for less than 40 percent (Hallmayer et al., 2011). This recent study highlights that while genetic factors play an important role, the role may be lower than previously estimated.

Family Studies

The study of family members of an individual with ASD has illuminated the potential role common genetic variation in the susceptibility to ASD. The broader autism phenotype has been observed in family members of individuals with ASD. Defined as having similar traits to ASD (such as aloofness, rigidity of thought, repetitive interests), but to lesser degree, the broader autism phenotype was identified in a large-scale study in 7.5% of relatives of in individuals with ASD while in only 2.5% of relatives with Down syndrome (Pickles et al., 2000). Similarly, the broader autism phenotype has been observed in 12–20% of siblings of children with ASD but in only 2% of siblings of children with developmental delays and observed more often in parents of children with ASD relative to parents of typical children or children with delays (Bailey et al., 1995; Baron-Cohen & Hammer, 1997; Bernier, Gerdts, Munson, Dawson, & Estes, 2012; Dawson, Webb, Wijsman, et al., 2005; Gerdts, Bernier, Dawson, & Estes, 2013; Losh et al., 2009). The observation of a broader phenotype suggests that relatives of individuals with ASD may be demonstrating a lesser variant a result of shared genes (Baron-Cohen & Hammer, 1997).

A large study of infant siblings of children with ASD indicated that 18.7% of younger siblings of individuals with ASD went on to develop ASD with risk increasing the more older siblings with ASD in the family (Ozonoff et al., 2011). In contrast, only approximately .18% of second-degree relatives and .12% of third-degree relatives of an individual with ASD also have ASD (DeLong & Dwyer, 1988;

Jorde et al., 1991; Pickles et al., 1995; Szatmari, Volkmar, & Walter, 1995). The differential rates of ASD in extended family members relative to siblings suggest that many genes may contribute to ASD (Pickles et al., 1995).

Genetic Findings

Early molecular studies of ASD focused on linkage analysis to identify potential genomic regions harboring ASD susceptibility gene or genes. Through these studies many chromosomal regions were identified, yet few were replicated reflecting the heterogeneity in genetic contributions (e.g., Barrett et al., 1999; IMGSAC, 1998; Philippe et al., 1999; Risch et al., 1999) and no single gene region has been reliably identified (Abrahams & Geschwind, 2008).

Research suggests that there is no single gene that accounts for ASD, but rather that there are multiple genes and structural rearrangements, each one a risk factor that may alone or in concert with other genetic variation, contribute to ASD (Folstein & Rosen-Sheidley, 2001). Indeed, approximately 10–30% of ASD cases have an identified genetic cause through an observable chromosomal structural rearrangement, called copy number variation (CNV), or gene mutation (Abrahams & Geschwind, 2008; Krumm, O'Roak, Shendure, & Eichler, 2014). Among individuals with an identified genetic contributor, the most common contributors are CNVs in regions 15q11–13 and 16p11.2, CNVs at each region accounting for only approximately 1% of cases (Miles, 2011). However, complicating the picture is that individuals with CNVs in these regions, such as 16p11.2, ascertained for the presence of the event, do not always develop ASD. In fact, ASD is only observed in 23% of individuals with 16p11.2 deletion (Hanson et al., 2014). With the advent of exome and targeted sequencing the discovery of disruptive gene mutations has advanced the understanding of genetic risk factors. Indeed, exome sequencing has yielded findings that close to 1,000 different genes may contribute to ADS (O'Roak, Vives, Girirajan, et al., 2012; Sanders et al., 2012). Among the most prominent are CHD8, DYRK1A, GRIN2B, PTEN, TBR1, TBLXR1, with mutations to these 6 genes likely contributing to 1% of all ASD cases (O'Roak, Vives, Fu, et al., 2012). Indeed, CHD8 appears to be the most common single gene mutation contributing to ASD and represents a distinct subtype of ASD with characteristic facial features, macrocephaly, and gastrointestinal disturbances (Bernier et al., 2014). Many other genes have been linked to ASD including ADNP (Helsmoortel et al., 2014), SCN2A (State & Sestan, 2012), SHANK2, SHANK3, and NLGN4 (Abrahams & Geschwind, 2008), which highlights the varied impacts on the development of the brain given the wide role on synaptic adhesion, chromatin modification, ion channel development, and the neurotransmitter receptors in which these genes are involved.

Our understanding of the genetics of ASD has advanced considerably since early twin studies, and these advances indicate ASD does not follow a simple pattern of inheritance and instead is the result of multiple genetic variants and mutations impacting a multitude of genes. Given the increased availability of high throughput sequencing and reduced cost for sequencing, a shift in the approach to studying the genetics of ASD has been proposed which entails the leveraging of technology to genetically classify individuals with ASD and then recontact and follow up for comprehensive evaluation to identify relevant behavioral subtypes and targets for treatment and intervention (Stessman, Bernier, & Eichler, 2014).

Environmental Risk Factors

Prenatal Risk Factors

A wide range of pre and perinatal complications has been associated with increased risk for ASD. Although no single prenatal factor has been associated with the etiology of ASD (Gardener, Spiegelman, & Buka, 2009), a large, population based study of environmental contributions of ASD suggested that fever during pregnancy increased the risk for ASD (Zerbo, Iosif, Delwiche, Walker, & Hertz-Picciotto, 2011). The proposed mechanism for this increased risk following maternal infections is that the immune response and maturational processes at critical developmental periods are disrupted (Hertz-Picciotto et al., 2008). It has also been reported that mothers with certain medical conditions, including diabetes (type 2 or gestational), chronic hypertension, or pre-pregnancy obesity was associated with increased risk for autism (Krakowiak et al., 2012). The authors hypothesize that metabolic disruption results in increased ASD risk. Rodent and non-human primate models mirror these findings of increased ASD susceptibility following maternal immune activation (M. D. Bauman et al., 2013; Malkova, Yu, Hsiao, Moore, & Patterson, 2012).

Other prenatal factors associated with ASD risk include exposures in utero to a variety of agents including thalidomide (Rodier, 2002; Stromland, Nordin, Miller, Akerstrom, & Gillberg, 1994), misoprostol (Bandim, Ventura, Miller, Almeida, & Costa, 2003), and valproic acid (Moore et al., 2000; Rasalam et al., 2005; Stromland et al., 1994). Across all of these exposures, the mechanism is based on reported observations of the teratogenic effects of these substances on neurodevelopment (Landrigan, 2010). More

recently, air pollution (Volk, Hertz-Picciotto, Delwiche, Lurmann, & McConnell, 2011; Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013) and agricultural pesticides (Eskenazi et al., 2007; Roberts et al., 2007; Shelton et al., 2014) have been associated with increased risk. The hypothesized mechanisms for these environmental pollutants are that thyroid hormones, which have been implicated in neurodevelopmental problems (Porterfield, 1994), are disrupted (Roberts et al., 2007) and that sex steroids are impacted, which have been proposed to account for the observed male to female ratio bias in ASD (Baron-Cohen, Knickmeyer, & Belmonte, 2005; Knickmeyer et al., 2006).

Use of prenatal folic acid supplements around the time of conception has been associated with decreased risk for autism (Suren et al., 2013). Research also suggests that the MTHFR C677T polymorphism is associated with increased ASD risk, and periconceptional folic acid may reduce ASD risk in those with MTHFR 677C>T polymorphism (Pu, Shen, & Wu, 2013).

Perinatal Risk Factors

A broad range of perinatal complications have been proposed to increase ASD risk, including breech presentation, umbilical cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, summer birth, low birth weight, small for gestational age, congenital malformation, low Apgar scores, feeding difficulties, meconium aspiration, neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia (Gardener, Spiegelman, & Buka, 2011). The relationship between the complication and ASD may be a function of the hypoxia associated with the event, which can impact central nervous system and later development. Elevated risk has also been found with non-elective C-sections, but it is likely a pre-existing condition necessitating the surgery as opposed to the surgery itself that increases ASD risk (Krakowiak et al., 2012). Additionally, a number of perinatal complications have not been found to associate with ASD, including use of anesthesia, post-term birth, and physical characteristics such as high birth weight and head circumference. Increased risk for autism has been associated with induced or augmented childbirth (Gregory, Anthopolos, Osgood, Grotegut, & Miranda, 2013). Further research is needed to explain this association which could be related to underlying pregnancy conditions required need to induce/augment as opposed an independent contributor of ASD risk.

In general, challenges to clarifying the extent and effects of these perinatal complications concern the interaction between birth complications and prenatal problems, making it difficult to determine the independent contribution of any of these factors to conferring ASD risk. For example, C-sections are more common in pregnancies with abnormal fetal presentation, fetal distress, and multiple births, preventing a clear understanding of the independent effect of any birth complication. Further research in this arena is needed.

Gene–Environment Interactions

An important area of investigation exists at the intersection between genetics and the environment, as it is likely that the etiology of many individuals with ASD is a function of both genetic and environmental factors (Newschaffer et al., 2007). This perspective is supported by the observation of abnormal neuroinflammation following infection in individuals with ASD and the potential role of gene disruptions related to DNA repair and immune and inflammatory response (Herbert et al., 2006) as well as the finding that individuals with a promoter variant to the MET gene who are prenatally exposed to environmental toxins are at increased risk above prenatal exposure and having the genetic variant alone (Volk et al., 2014). Another gene environment interaction is reflected in the finding that increased paternal age confers ASD risk potentially by the alteration in the germ cells as a result of accumulated exposure to environmental toxins over the lifetime (Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2011). Given the recent advances in genetics of ASD and the scrutiny of the environment contributions to the disorder, the examination of the intersection of the two factors will be at the forefront of the research agenda in the coming years.

BRAIN STRUCTURE AND FUNCTION

Studies employing brain autopsies, structural and functioning imaging, and electroencephalography all converge to indicate atypical brain structure and function in ASD. Neuroanatomical findings, in general, conclude that ASD is marked by structural enlargement in some brain regions and reduction in other areas (see Koenig, Tsatsanis, & Volkmar, 2001, for a review). Although seemingly contradictory, these finding suggest that across the many etiologies of ASD, abnormal cell growth during the early

stages of prenatal and postnatal brain development may be the common underlying etiological mechanism. That is, in contrast to typical brain development in which neurons proliferate and become interconnected and then are pruned through experience and development, in ASD, the process of neural growth and pruning may be disrupted resulting in size differences across neuroanatomical structures (Minshew, 1996). Imaging studies show increased overall brain volume (Courchesne et al., 2001; Hazlett et al., 2011; Piven, Arndt, Bailey, & Andreasen, 1996; Piven et al., 1995; Schumann et al., 2010; Sparks et al., 2002) and autopsy studies report increased brain weight (Bailey et al., 1998; Bauman & Kemper, 1994). These findings are supported by studies of head circumference that demonstrates rapid, early growth in ASD (Chawarska et al., 2011; Courchesne, Campbell, & Solso, 2011; Courchesne & Pierce, 2005a; Dawson et al., 2007; Elder, Dawson, Toth, Fein, & Munson, 2008). Enlargement of both white and gray matter appears to account for this rapid growth (Hazlett et al., 2011; Schumann et al., 2010), but a large study of brain growth in teens and young adults suggests that atypical decline may occur at these ages as well (Courchesne et al., 2011). In addition to the observation of atypical brain growth in ASD, several specific brain regions have been implicated, including the cerebellum, the limbic system, several systems in the cerebral cortex, and corpus callosum. The specific regions and structures are outlined in Table 3.3.

Cerebellum

Studies employing different experimental methods have identified atypical structure and function of the cerebellum in ASD. Structural MRI studies report enlarged cerebellar volume (Carper & Courchesne, 2000; Courchesne, Redcay, Morgan, & Kennedy, 2005), magnetic resonance spectroscopy (MRS) studies indicate decreased concentrations of neural substrates indicating diminished cerebellar functioning (Chugani, Sundram, Behen, Lee, & Moore, 1999; DeVito et al., 2007), and functional MRI studies demonstrate atypical activity in the cerebellum during attention and motor tasks (Allen, Müller, & Courchesne, 2004). Similarly, postmortem studies in ASD have found a loss of Purkinje and granule cells in the region of the cerebellum that receives auditory and visual information (Bailey et al., 1998; Bauman & Kemper, 1985; ML Bauman & Kemper, 1988; Carper & Courchesne, 2000; Palmen, van Engeland, Hof, & Schmitz, 2004; Whitney, Kemper, Bauman, Rosene, & Blatt, 2008). Two proteins implicated in cell migration and pruning, Reelin and Bcl-2, are reportedly decreased in cerebellar tissue (Fatemi, Stary, Halt, & Realmuto, 2001).

TABLE 3.3 Brain Regions and Structures Implicated in in ASD and Their Purported Function

Brain area	ASD-related domain	Proposed function	Citation
Ventromedial prefrontal cortex	Social communication	Social decision making	Carper and Courchesne (2005)
Orbitofrontal cortex	Social communication	Adaptive learning through stimulus–reinforcement association	Girgis et al. (2007)
Anterior cingulate cortex	Social communication	Social orienting, initiation, motivation, goal-directed behaviors	Mundy (2003)
Inferior frontal gyrus	Social communication	Imitation, language production	Dapretto et al. (2006)
Posterior parietal cortex	Social communication	Imitation, understanding goals and intentions	Williams et al. (2006)
Fusiform gyrus	Social communication	Face perception and processing	Schultz et al. (2000)
Superior temporal sulcus	Social communication	Biological motion perception, understanding goals and intentions	Pelphrey and Carter (2008)
Amygdala	Social communication	Assignment of emotional valence, emotional learning	Baron-Cohen et al. (2000)
Basal ganglia	Repetitive and restricted behaviors	Compulsive behaviors, repetitive motor behaviors, routines	Langen, Durston, Staal, Palmen, and van Engeland (2007)
Substantia nigra	Social communication/Repetitive & restricted behaviors	Reward, reinforcement, and motivation	Lewis, Tanimura, Lee, and Bodfish (2007)
Thalamus	Social communication/Repetitive and restricted behaviors	Sensory-motor integration	Tsatsanis et al. (2003)
Cerebellum	Social communication/Repetitive and restricted behaviors	Engagement and disengagement of attention	Courchesne (1997)
Hippocampus	Social communication	Learning and memory	Bauman and Kemper (2005)

The findings of atypical cerebellar functioning mirror some of the atypical behaviors and skills observed in ASD that have been associated with the cerebellum. For example, many individuals with ASD have difficulties with sequencing language, motor movements, and shifting attention. These abilities are partially mediated by the cerebellum. Importantly, the ability to shift attention is critical for joint attention, theory of mind, and the ability to transition from one activity to another, all symptoms associated with ASD (Carper & Courchesne, 2000; DiCicco-Bloom et al., 2006; Gillberg, 1999).

The Amygdala

Evidence for disruptions in the amygdala and hippocampus in ASD follows from early findings of decreased neuronal cell size in these structures (Bauman & Kemper, 1988, 2005; Schumann & Amaral, 2006). Studies have found increased amygdala size (relative to total brain volume) in ASD with more severe symptoms (Schumann, Barnes, Lord, & Courchesne, 2009; Schumann et al., 2004; Sparks et al., 2002) although findings reveal a relationship with age and the amygdala (Stanfield et al., 2008). Size differences are not found in older children and adults (Aylward et al., 1999; Haznedar et al., 2000; Nacewicz et al., 2006) suggesting the growth observed in middle childhood in typical development does not occur in ASD (Amaral, Schumann, & Nordahl, 2008). Interestingly, enlargement of the amygdala in toddlerhood is predictive of more significant impairment trajectory in ASD between 3 and 6 years of age (Munson et al., 2006). Two competing hypothetical mechanisms have been proposed to account for the amygdala findings in ASD: either fewer neurons are generated in early development or an excessive number are but there is subsequent elimination of those neurons (Amaral et al., 2008).

Corpus Callosum

The wide band of nerve fibers linking the left and right hemispheres of the brain appears to be reduced in size in children and adults with ASD (Alexander et al., 2007; Boger-Megiddo et al., 2006; Egaas, Courchesne, & Saitoh, 1995; Hardan, Minshew, & Keshavan, 2000; Manes et al., 1999; Piven, Bailey, Ranson, & Arndt, 1997; Vidal et al., 2006). This observed size difference in these white matter tracts in ASD supports the theory that disruptions to cortical connectivity may play a role in ASD. Increased white matter has been observed throughout the brain with the frontal lobe white matter showing the greatest increase (Courchesne et al., 2001; Hazlett et al., 2005; Herbert et al., 2004) implicating a deficit in regional or hemispheric brain communication (Belmonte et al., 2004; Courchesne & Pierce, 2005b; Just, Cherkassky, Keller, & Minshew, 2004; Penn, 2006; Rippon, Brock, Brown, & Boucher, 2007).

Cortical Regions

Imaging and neurophysiological studies indicate abnormal development and functioning of a number of cortical regions. Consistent atypicality has been reported in the prefrontal cortex (Carper & Courchesne, 2000; Courchesne et al., 2005; DeVito et al., 2007). Dysfunction and thinning in the frontal lobes has been associated with theory of mind (F. Happe et al., 1996), imitation impairments (Dapretto et al., 2006), and executive functioning (Gilbert, Bird, Brindley, Frith, & Burgess, 2008). Other cortical regions have been proposed to be involved in ASD including the fusiform gyrus, implicated in functional imaging and neurophysiological studies of face processing (Dawson et al., 2002; Dawson, Webb, et al., 2004; Kleinhans, Muller, Cohen, & Courchesne, 2008; Schultz, 2005; Webb et al., 2006), and the superior temporal sulcus, implicated in perception of biological motion and intention understanding (Pelphrey, Morris, & McCarthy, 2005; Pelphrey, Adolphs, & Morris, 2004). The parietal lobe has been implicated as well through imaging and neurophysiological studies, consistent with the proposal of mirror neuron dysfunction in ASD (Bernier et al., 2007; Oberman & Ramachandran, 2007; Williams et al., 2006).

INTERVENTIONS AND TREATMENT

Pioneering work in the ’60s and ’70s adopted behavioral principles in the treatment of ASD (Berkowitz & Graziano, 1972; Hingtgen, Coulter, & Churchill, 1967; Leff, 1968; Lovaas, Schreibman, & Koegel, 1974; Mazuryk, Barker, & Harasym, 1978) and following the publication of Lovaas’s (1987) controlled intervention trial based on the principles of applied behavioral analysis (ABA), the notion that ASD could be treated was ushered into the professional and parent community. In the years since this early work, major advances in ASD intervention have been made, by building upon behavioral principles, incorporating naturalistic approaches, and embracing a developmental framework. Additionally, myriad psychopharmacological as well as complementary and alternative approaches have been developed and are currently in use in the treatment of ASD. However, large scale RCTs evaluating the efficacy

of autism interventions are still lacking (Warren et al., 2011). Despite this, with the advent of intervention there have been significant improvements in the outcomes for children with ASD with a minority of children actually losing symptoms altogether and achieving functioning within the normal range (Fein et al., 2013).

Behaviorally Based Intervention Models

Interventions based on ABA principles have garnered the most empirical support in the treatment and management of ASD (National Research Council, 2001). Multiple studies have replicated Lovaas's (1987) findings of efficacy (Cohen, Amerine-Dickens, & Smith, 2006; Howard, Sparkman, Cohen, Green, & Stanislaw, 2005; Sallows & Graupner, 2005) and long-standing gains have been observed (McEachin, Smith, & Lovaas, 1993). Indeed, one review of outcomes of 373 children in 13 studies indicated significant gains in cognitive ability following ABA based treatment (Reichow & Wolery, 2009). ABA based treatments have been shown to improve abilities across ASD domains including social communication and challenging behavior (Cohen et al., 2006; Horner, Carr, Strain, Todd, & Reed, 2002; McConnell, 2002; Sallows & Graupner, 2005).

Improved understanding of child development and the importance of generalizability of skills have led to the establishment of several naturalistic developmental models. Pivotal Response Training (PRT) is a naturalistic model that focuses on "pivotal" behaviors, such as motivation. Studies of PRT indicate improvement in social communication and play following intervention (Boettcher, 2004; Koegel, Carter, & Koegel, 2003; Koegel, Koegel, Shoshan, & McNerney, 1999; Koegel, Camarata, Koegel, Ben-Tall, & Smith, 1998; Schreibman, Stahmer, & Pierce, 1996). The Social Communication, Emotional Regulation, and Transactional Support model (SCERTS model) focuses on the specific learning styles to address the core deficits of children with ASD (Prizant, Wetherby, Rubin, & Laurent, 2003; Prizant, Wetherby, Rubin, Laurent, & Rydell, 2005). Kasari and colleagues (2006) have developed joint attention training to improve language and overall outcomes in ASD by addressing this precursor skill to so many core deficits in ASD. A randomized controlled trial of the 6-week intervention suggests improvements following treatment that persist 5 years later (Kasari, Gulsrud, Freeman, Paparella, & Hellemann, 2012) and that can be observed when administered in community preschool programs (Lawton & Kasari, 2012).

The Early Start Denver Model (ESDM), a downward extension of the Denver Model (Rogers et al., 2006; Rogers & Lewis, 1989), is a comprehensive developmental model based on ABA principles. A randomized, controlled trial of 48 toddlers demonstrated significantly greater improvement across cognitive, language, social, and adaptive domains for the ESDM group relative to the children receiving treatments in the community (Dawson et al., 2010). Further, following the 2 years of intensive intervention the children receiving the ESDM intervention showed normalization of brain activity in response to viewing faces and houses using EEG (Dawson et al., 2012), suggesting that this model significantly impacted not only behavior but also neurological functioning.

Pharmacological Intervention

Between 30 and 70% of children with ASD are prescribed medication in the course of their treatment (Aman, Lam, & Collier-Crespin, 2003; Aman, Lam, & Van Bourgondien, 2005; Esbensen, Greenberg, Seltzer, & Aman, 2009) although there are currently no medications that have demonstrated efficacy for addressing the core symptoms in ASD. The two FDA approved medications showing efficacy in ASD, risperidone and aripiprazole, target challenging behaviors and hyperactivity but not ASD itself (Marcus et al., 2009; Owen et al., 2009; Scahill et al., 2012). A comprehensive review of medical treatments in ASD indicates that most pharmacological interventions have limited evidence for their efficacy and those that do have been supported by private pharmaceutical companies. Further, no studies compare medical interventions to behavioral interventions or include combinations of both, even though most children with ASD receive both types of treatment (McPheeters et al., 2011).

Despite the limited extant literature, there are novel biomedical treatments under evaluation, such as arbaclofen, to address the core social deficits in ASD (Gurkan & Hagerman, 2012). Recent studies of oxytocin suggest promise (Domes et al., 2013) and indicate that even a single intranasal injection of oxytocin appears to normalize brain functioning and may therefore be an appropriate tool to bootstrap or enhance the effectiveness of behaviorally based interventions (Gordon et al., 2013).

Complementary and Alternative Approaches

Complementary and alternative treatments (CAT), defined as "medical and health care systems, practices, and products that are not generally considered to be part of

conventional medicine" (National Center for Complementary and Alternative Medicine, 2012), are commonly used in ASD with reports of between 32 and 80% of families reporting using or having used CAT to address ASD symptoms (Harrington, Rosen, Garnecho, & Patrick, 2006; Levy & Hyman, 2003; Levy, Mandell, Merhar, Ittenbach, & Pinto-Martin, 2003; Wong & Smith, 2006). This diverse group of treatments includes biomedical approaches, such as vitamins, supplements, diets, and procedures such as neurofeedback; mind–body interventions, such as meditation; body-based methods, such as massage; energy based treatments, including reiki; or alternative care systems (e.g., homeopathy) and the primary reported rationale for applying these approaches relate to safety concerns or adverse medication side effects (Hanson et al., 2007). Despite the widespread availability and application of CATs, there is limited scientific evidence supporting the efficacy of these approaches due to a lack of controlled trials, rigorous protocols, adequate sample sizes, clear inclusion criteria, and double blind designs (Lofthouse, Hendren, Hurt, Arnold, & Butter, 2012).

Many CATs have few or no studies examining their efficacy providing insufficient evidence in which to evaluate them; however, some have been studied using more rigorous designs. Melatonin is among the best-studied CAT for ASD and despite limitations to study designs, sample sizes, and variability in approaches, the existing literature suggests the use of melatonin holds promise for addressing sleep problems in ASD (Rossignol & Frye, 2011). Another well-studied CAT is Secretin. It has consistently been shown to have no utility in the management of ASD (Krishnaswami, McPheeters, & Veenstra-Vanderweele, 2011). Following media reports of its efficacy in a small group of children with ASD and diarrhea, excitement over Secretin as a treatment preceded the research, and only after dozens of studies failing to show efficacy was Secretin removed from favor (Schreibman, 2005). Other treatments that have failed to demonstrate positive effects through randomized controlled trials include auditory integration therapy (Sinha, Silove, Wheeler, & Williams, 2004), facilitated communication (Mostert, 2001), hyperbaric oxygen therapy (Jepson et al., 2011), and gluten/casein-free diet (Millward, Ferriter, Calver, & Connell-Jones, 2008). Countless other approaches still have insufficient evidence with which to evaluate their effectiveness, including many specific vitamin supplements, immune therapies, and movement therapies (Lofthouse et al., 2012). In total, although few specific CATs have sufficient evidence for effectiveness, it has been suggested that families work with their primary medical provider together to consider and perhaps utilize CATs that show potential promise, sensible rationale for effectiveness, fit with family's values, and show evidence for safety (Hendren, 2013).

FUTURE DIRECTIONS

Major advances in our understanding of ASD have been made in the intervening years since Leo Kanner first defined the disorder in 1943. It is clear now that ASD can be conceptualized as a group of disorders with significant heterogeneity in terms of etiology, course, response to treatment, and outcome. Developmental research has illuminated the core social impairments in ASD and provided insight into the downstream effects of these deficits on clinical presentation. Studies have also demonstrated the viability and importance of detecting ASD very early in development and identified several genetic and environmental contributors and risk factors. Investigations in neuroanatomy and function indicate atypical growth and disruption to a range of structures and regions and the focus on intervention has shown that although all children with ASD benefit from intervention, some clear show rapid gains while others show slower response. Future directions in ASD research will expand on these gains. The identification of biomarkers to be used in early detection of ASD is a key focus of research and will allow for earlier application of intervention focused on the core deficits in ASD. By addressing these core deficits earlier, developmental trajectories can be normalized and outcomes optimized. Studies focused on etiology will address the heterogeneity of ASD by continuing to clarify the contributions of specific ASD associated genes and environmental risk factors. Future treatment research will likely entail more rigorous analysis of complementary and alternative approaches, the discovery of novel pharmacological agents or novel application of existing medications, careful identification of the mediators and moderators of treatment response for all treatment types, and the matching of treatments for specific, etiologically linked ASD subtypes. Ultimately the future holds the potential for bridging our understanding of early detection, etiology, and treatment such that biomarkers can be used to identify children at risk for ASD, so that relevant, targeted treatments based on etiological subgroups can be applied to improve outcomes for individuals with ASD.

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CHAPTER 4

Joint Attention and the Social Phenotype of Autism Spectrum Disorder: A Perspective From Developmental Psychopathology

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OVERVIEW

This chapter describes one way translational research has changed how we think about, diagnose, and treat the social impairments of autism spectrum disorder (ASD). It also relates the story of how the application of developmental science to the study of ASD has encouraged new ways of thinking about the typical development of human social cognition. In particular, human social cognition may be viewed as the outgrowth of a special form of human information processing that we call joint attention (Mundy & Newell, 2007). This chapter will describe how joint attention is more than a milestone in the development of social cognition in infancy. Rather, it is an executive form of information processing that contributes to social learning, stimulus encoding, and the facilitation of human social communication and connectedness across the life span. This executive joint attention function integrates information about oneself, other people, and shared attention to objects, events, or ideas. It does so through the integrated activation and functions of a distributed system of frontal and posterior cortical networks in the brain. Recognizing and understanding the parallel and distributed nature of executive joint attention functions contributes to new perspectives about the nature and development of social cognition and about the nature of the social brain in all people, including those affected by ASD (Mundy, 2003). This new framework has emerged from the

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[1]Color versions of Figures 4.3, 4.7 and 4.11 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

interplay between cognitive neuroscience, developmental science, and the science of autism. It integrates the idea that a "developmental analysis" (Cicchetti & Toth, 2009, p. 16), which underscores the importance of developmental timing, multiple determinants of behavior, and multiple pathways to positive or negative outcomes, is necessary to fully understand the impact of joint attention disturbance on development. As such, it provides a seminal illustration of a school of translational research that began three decades ago when a farsighted group outlined the new discipline of *developmental psychopathology* (Cicchetti, 1984; Sroufe & Rutter, 1984).

The chapter begins with a brief historical review of the conceptualization of ASD. One key message is that a lack of precise understanding of the typical developmental trajectory of social behavior impeded the accurate diagnosis of ASD until the early 1990s, which was 50 years after it was initially described by Asperger (1944) and Kanner (1943). Then we provide a review of the typical development of joint attention, the underlying neural systems supporting its development, and the utility of adopting a dynamic systems approach in understanding the neurocognitive development of joint attention. Following that review, we discuss the relation between social impairment and joint attention in ASD. This review also illustrates how social developmental research continues to be a vital source of information about the nature of ASD, and how research on ASD has led to insights about the precise nature of the typical development of joint attention in infants that have contributed to the framework for a new model of human social cognition development. As previously noted, this chapter adopts a parallel and distributed information processing perspective on joint attention and social cognition. An advantage of this model is that it explicitly attempts to link developmental behavioral research on social pathology to a range of recent observations, from research on neural connectivity and genetics, ocular motor control, and intervention in autism, discussed in the final section of the chapter.

A HISTORICAL PERSPECTIVE ON AUTISM SPECTRUM DISORDER

ASD is a biologically based condition that is characterized by impaired social development, impaired language, or pragmatic communication skill acquisition, and the presence of repetitive behaviors and thoughts (Asperger, 1944; Bailey, Philips, & Rutter, 1996; Dawson, Osterling, Rinaldi, Carver, & McPartland, 2001; Kanner, 1943). The symptoms of ASD in many affected children are observable by 24 months of age or earlier (Stone, Coonrod, & Ousley, 1997; Zwaigenbaum et al., 2005), with children expressing different courses of symptom onset. Some children may display clear symptoms by the end of the first year or early part of the second year of life. Other children may display more typical development through the first year but then not display the typical rate of advances in social communication behaviors in the second year, while others may display a second year course more indicative of the interruption or loss of elements of social communication development (Ozonoff, Heung, Byrd, Hansen, & Hertz-Picciotto, 2008).

Leo Kanner (1943) displayed impressive clinical acumen when he was able to discern three common characteristics that distinguished children with ASD from those in a larger clinical sample of children with varied exceptionalities. He noted that children with ASD appeared to have (1) a common impairment of affective relatedness to others, which (2) resulted in a disorder that primarily involved impairments of the capacity for typical social interactions and (3) was most likely caused by biologically based processes. The recognition of the biological, affective, and social-behavioral syndrome triumvirate of autism was a remarkable achievement and is as valid today as it was in 1944. Unfortunately, Kanner's initial perspective did not fit well with the psychodynamic zeitgeist of the time. The psychodynamic perspective of the time emphasized the primacy of environmental over biological factors in the etiology of all psychopathology. Sufficient challenges were brought to bear in this regard that Kanner (1949) recanted in his initial biological view of ASD.

In the ensuing thirty years, the science of autism drifted from one perspective to another. ASD was described as a disorder caused by an aloof parenting style that caused children to grow up to be severely emotional disengaged from all people (Bettleheim, 1959). By the early 1960s, compelling indirect evidence for the biological nature of ASD had been presented to counter this parenting style hypothesis (e.g., Rimland, 1964). However, the singular prototype of people with ASD as emotionless and aloof remained for a long time. Few data were available to critically appraise prototype because the social and emotional development of children with ASD was rarely a focus of empirical inquiry through the 1970s. For example, Pat Howlin (1978) required only seven pages and 39 citations to review the literature on the social behavior of children affected by ASD at the time. Moreover, only a handful of the citations referred to peer-reviewed empirical research publications on the social behavior of ASD. Alternatively,

research and theory at that time was taken with the notion that sensory, perceptual, or language impairments must be primary to the phenotype and etiology of ASD (Mundy & Sigman, 1989). Although this was a scientifically valid assumption given the dearth of any appreciable empirical research on autism, it had the untoward consequence of relegating social-emotional impairments to the status of epiphenomenon in models of ASD. The secondary status of social-emotional symptoms constrained the theory and methods used to establish the initial diagnostic criteria for ASD.

DIAGNOSTIC DESCRIPTION OF ASD

The first attempts in the USA to establish a systematic diagnostic definition of ASD were in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III;* American Psychiatric Association, 1980). *DSM-III* described only six symptom criteria for the diagnosis of autism: (1) onset before 30 months of age; (2) a pervasive lack of responsiveness to other people; (3) gross deficits in language development; (4) if speech is present, peculiar speech patterns such as immediate and delayed echolalia, metaphorical language, pronominal reversal; (5) bizarre responses to various aspects of the environment, (e.g., resistance to change, peculiar interest in or attachments to animate or inanimate objects); and (6) absence of delusions, hallucinations, loosening of associations, and incoherence as in schizophrenia.

The item in this initial set of symptoms that was specific to the social deficits of autism was the rather broad and vague descriptor of a pervasive lack of responsiveness to other people. There had been so little research on defining the nature of the social deficits of autism through 1980 that we simply had no idea how to precisely describe this symptom domain of ASD, even though Kanner had argued that it was the central symptom domain of the syndrome. Fortunately, in the subsequent decade there was a virtual explosion of research on the social-deficits of ASD. Indeed, when Pat Howlin published a second review of research on the social development of ASD, eight years after her first effort in 1978, she required 24 pages and 116 citations to adequately cover the field (Howlin, 1986).

This welcome increase in information on the social nature of ASD occurred because of translational research. Several groups in the United States, the United Kingdom, and throughout the world began to recognize that theory and methods used in the study of human infancy and primate social development could be used as powerful tools to examine and define the social deficits of ASD (e.g., Baron-Cohen, Leslie, & Frith, 1985; Cicchetti, 1984; Dawson & McKissick, 1984; Rogers & Pennington, 1991; Sigman & Ungerer, 1984; Wimmer & Perner, 1983); more recently, there has been acknowledgement that the social deficits of ASD may provide important insights on typical development, as well (Cicchetti & Toth, 2009). This new wave involved the translation of the basic developmental science studies of infant imitation, social learning, social cognition, preverbal communication, and attachment, as well as social cognitive development in young children. One fairly immediate and vital impact of this surge of translational research was the dawning awareness that the description of the social impairments of ASD singularly as a *pervasive lack of responsiveness to others* was at best limited and, at worst, misguided. That description established an ASD prototype of a completely socially unresponsive child, but empirical research indicated that this prototype did not effectively characterize the spectrum of children that were affected by the syndrome (Mundy & Sigman, 1989; Wing & Gould, 1979).

One of the most fundamental observations in the science of autism is that the expression of the social phenotype of ASD varies across children (Wing & Gould, 1979). Wing and Gould (1979) found that some children with ASD appeared to be socially aloof, much as the description of "a pervasive lack of responsiveness" suggests. These aloof children often performed in the severe or moderate range of intellectual disabilities on measures of IQ or developmental status. However, many other children with mild intellectual disabilities or IQs in the typical range were not pervasively underresponsive. Instead, some were passive but socially responsive in structured situations. Other children were even proactive in initiating interactions. However, while socially more active, these children displayed social behavior that was odd, atypical, and frequently maladaptive in engaging or maintaining interactions with other people (Fein et al., 1999; Volkmar, Cohen, Bregman, Hooks, & Stevenson, 1989; Wing & Gould, 1979).

In addition to the recognition of the Wing and Gould tripartite social typology of ASD, by the end of the 1980s, studies had reported the observation that many children with ASD displayed patterns of social strengths, as well as weaknesses, rather than only a pattern of a *pervasive lack of responsiveness to other*s. For example, children with ASD responded when others imitated them, and some children appeared to learn from observing social modeling. Many children reportedly increased their social behaviors in structured situations, and children with ASD varied greatly in their use of gestures and eye contact

to communicate (Curcio, 1978; Lewy & Dawson, 1992; Mundy & Sigman, 1989). Perhaps most remarkably, children with ASD often displayed levels of attachment behaviors that were commensurate with their mental development and *not atypical* relative to other groups of children with comparable developmental delays (Mundy & Sigman, 1989; Shapiro, Sherman, Calamari, & Koch, 1987; Sigman & Ungerer, 1984). In these studies, measures of attachment were used that assessed children's responses to separations, and, especially, reunions with their caregivers. Many children with ASD displayed behaviors that suggested they had developed emotional bonds that were specific to their caregivers and that supported the children's self-regulation in a strange laboratory environment. Such displays of social bonding to caregivers were wholly inconsistent with many of the then current models of ASD, including the notion that all affected children displayed a universal lack of responsiveness to others.

Consequently, by the early 1990s translational developmental research indicated that key elements of the nosology of ASD were incorrect. Children with ASD, as a group, did not display a *pervasive* lack of responsiveness to others. Not only was this inaccurate, it promoted a constricted view of ASD that excluded many children with the syndrome who frequently made eye contact, or displayed caregiver attachment, or any of a number of other social abilities. The persistence of this inaccurate taxonomic prototype likely contributed to a historic underestimation of the prevalence of ASD (Wing & Potter, 2002). Indeed, only with the publication of the fourth edition of the *DSM*, in 1994, did we begin to have sufficiently well-defined guidelines that both accurately captured something of the essence of the core social impairments of ASD, and acknowledged the range of phenotypic variability expressed across individuals with this syndrome. Prior to this, in the 1970s, 1980s, and early 1990s, we simply could not identify all the children with ASD in the population because we limited ourselves to those that just met a very limited and restrictive social criterion.

Research-based revisions of social diagnostic criteria of ASD by both the American Psychiatric Association (APA, 1994, 2000, 2013) and the International Classification of Disease (ICD), established by the World Health Organization (1991), have led to more effective and informed ASD identification and diagnosis. In the most recent revision (*DSM-5*; APA, 2013), the persistent impairment in social communication and interaction in ASD became defined in terms of the expression of the following symptoms: (1) deficits in social-emotional reciprocity, ranging from abnormal social approach and failure of normal back-and-forth conversation to reduced sharing of interests, emotions, or affect, to failure to initiate or respond to social interactions; (2) deficits in nonverbal communicative behaviors used for social interaction, ranging from poorly integrated verbal and nonverbal communication to abnormalities in eye contact and body language or deficits in understanding and use of gestures, to a total lack of facial expressions and nonverbal communication; (3) deficits in developing, maintaining, and understanding relationships, ranging from difficulties adjusting behavior to suit various social contexts to difficulties in sharing imaginative play or in making friends to absence of interest in peers.

"Deficits in relationships, or lack of sharing imaginative play or in making friends" as a symptom item is extremely useful, but not until children reach 3 or 4 years of age. As a result, the early identification and diagnosis of the social deficits of ASD relies on observation of the other social symptoms, which heavily draw from the concept of joint attention. Thus, this chapter attempts to provide a detailed consideration of why joint attention, operationalized as sharing interests, emotion, or affect, or initiating or responding to other people, via eye contact and nonverbal communication, is central to the description of the social pathology of ASD, and the very nature of this syndrome.

JOINT ATTENTION IN TYPICAL DEVELOPMENT

Well before infants learn to use symbols and language, they begin to spontaneously share information with other people. They do so by coordinating their attention with another person and by using eye contact and gestures to show objects to others, as well as to request objects or events (Bates, Benigni, Bretherton, Camaioni, & Volterrra, 1979). In a seminal paper in *Nature,* in 1975, Scaife and Bruner reported that between 6 to 18 months of age infants increasingly displayed the ability to follow the direction of gaze of a social partner. When a tester turned her head to the left or right many infants tracked and followed the visual attention of the tester with their own line of regard. This observation was groundbreaking. It was inconsistent with the prevailing notion of egocentrism or the idea that infants could not adopt dual perspectives, such as the perspective of self and another person, until late in the second year (Piaget, 1952). Scaife & Bruner's (1975) observations suggested that infants begin to differentiate information about their own visual perspective and that of another person, and then align their perspective with another person's much earlier in life than that.

Bruner (1975) adopted the general term *joint attention* for this domain of infant development. He recognized that this ability allowed infants and caregivers to adopt co-reference to the same object or event, and that this ability was a milestone in human social learning. One of Bruner's goals was to understand how young children learn, in order to improve early educational curriculums. Instead of studying only how knowledge was acquired (learning), he studied how the ability to share knowledge in social learning develops because this is essential to all forms of pedagogy. His work suggested that the development of the ability to participate in joint attention marked a critical turning point in some unknown set of early cognitive processes that enabled young children to more effectively benefit from caregiver scaffolding. Indeed, the emergence of joint attention ability in infants may even elicit or promote scaffolding in caregivers, suggesting that a multiple-level, bidirectional analysis of joint attention behavior in dyads would be necessary to fully understand the process (Cicchetti & Toth, 2009). Bruner, along with others before him (e.g., Werner & Kaplan, 1963), understood that the development of the capacity to adopt a common point of view (shared reference) was elementary to our human ability to perceive shared meanings and necessary for the development of symbolic thinking and language development.

Measurement of Subtypes of Joint Attention

In the early days of research, it became apparent that infants did not just develop one type of joint attention behavior. Rather, the development of joint attention was expressed in different functional forms in infancy (Bates et al., 1979). Infants may *respond* to others' joint attention bids or *initiate* joint attention bids (Seibert, Hogan, & Mundy, 1982). They do so to share declarative or imperative information about an object or event (Bates et al., 1979). In the declarative function, infants use their line of regard and gestures to share their experience of an object or event (e.g., interest) with another person, or they respond to others' attempts to indicate their experience of an object or event. These two types of behaviors came to be known as initiating joint attention (IJA) and responding to joint attention (RJA), respectively (Seibert et al., 1982). Current data supports the observations of Scaife and Bruner (1975) and indicates that infants begin to reliably turn their head or eyes to follow the visual line of regard of another person by 6 months of age (Gredebäck et al., 2010; Figure 4.1a). Less is known about the development of IJA, but data suggest that the ability to alternate eye contact between an object or event and another person, to spontaneously share interest or experience with a social partner, is well developed in many 8–9-month-olds (Bates et al., 1979; Mundy et al., 2007; Figure 4.1b, Figure 4.1c).

The declarative, social sharing functions of IJA and RJA can be juxtaposed with other behavior that involve establishing a common point of reference with other people for instrumental and imperative purposes (Bates et al., 1979). By 9 months of age, infants direct the attention of other people to express their desires (e.g. request) for an object or event using initiating behavioral requests (IBR; Figure 4.1d). In addition, they learn to respond to the attention directing bids that adults use to request objects or actions from infants. This is referred to as responding to behavioral requests (RBR; Figure 4.1e).

The theory and measurement concerning infant joint attention in the 1970s and 1980s interacted with the contemporary concern with identifying valid infant markers of individual differences in cognitive development. The types of sensory motor measures then used to assess infant intelligence and cognitive risk at the time were not sufficiently reliable or valid (Lewis & McGurk, 1972). Without valid measures, it was challenging to identify many infants who were at risk for developmental disorders. It was also difficult to know what constituted valid targets for early cognitive intervention. This impasse began to clear as applications of basic research indicated that measures of infant visual attention could be used as valid indicators of current and future cognitive development in infancy (Bornstein & Sigman, 1986). Although not fully appreciated at the time, this assertion could be expanded to include measures of infant *joint attention* development (Sigman & Mundy, 1993).

One laboratory for research on infant attention was created by Jeff Seibert and Anne Hogan at the Debbie School of the University of Miami. The Debbie School served preschoolers who had moderate to severe motor and developmental impairments. Their motor impairments made the use of sensorimotor cognitive assessments and interventions extremely impractical. So Seibert, Hogan, and their graduate student began to develop an early assessment and intervention curriculum that focused on joint attention and preverbal communication skill development. This resulted in the Early Social Communication Scales (ESCS), which organized precise observations of joint attention and social attention coordination into a measurement instrument that could also be used to guide early intervention (Seibert, Hogan, & Mundy, 1982). A lasting contribution of the ESCS, along with related measures (Stone, Coonrod, & Ousley, 1997; Wetherby, Allen,

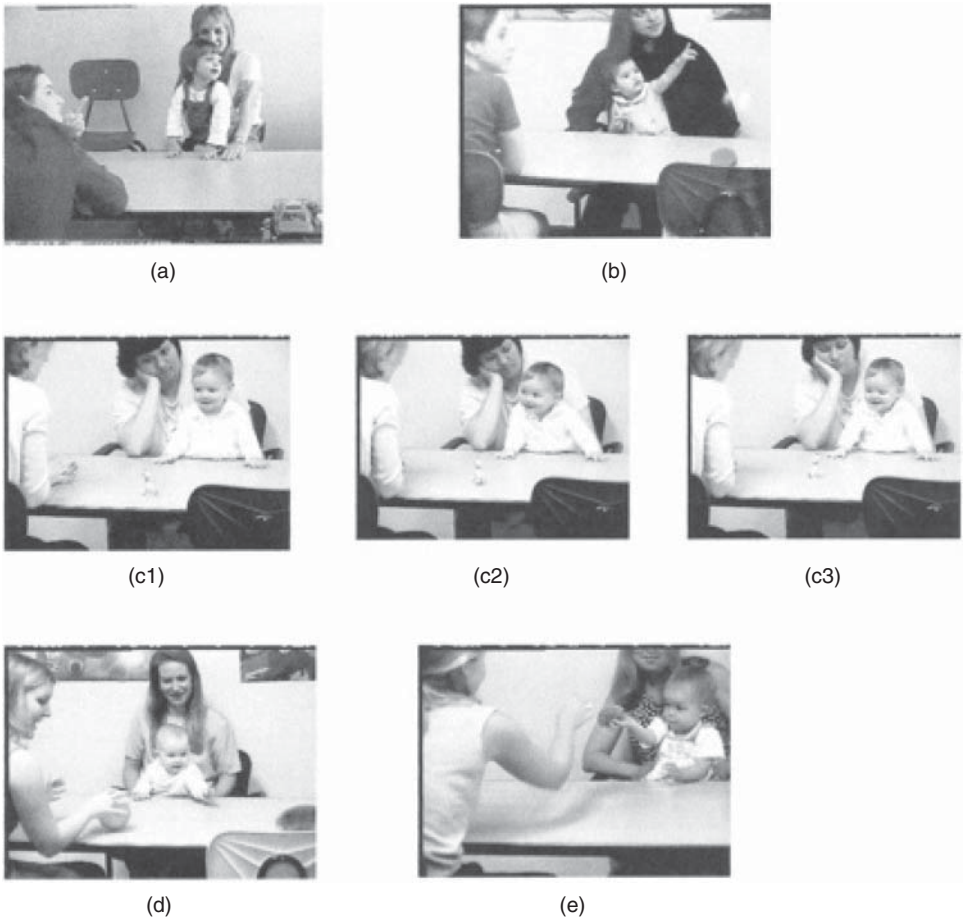


Figure 4.1 Illustrations of different types of infant social attention coordination behaviors: (a) responding to joint attention (RJA): following another person's gaze and pointing gesture; (b) initiating joint attention (IJA): using a conventional gesture (such as pointing) to share attention regarding a room poster; (c1,2,3) IJA: using an alternation of eye contact to share attention with respect to a toy; (d) initiating behavior requests: pointing to elicit aid in obtaining an out of reach object; (e) responding to behavior requests: following an adult's open-palm give-it-to-me gesture.

Cleary, Kublin, & Goldstein, 2002) was that joint attention assessment turned out to be a powerful instrument for the study of ASD and individual differences in social learning capabilities.

Learning and the Importance of Joint Attention

Early language learning often takes place in unstructured, incidental situations where parents spontaneously refer to a new object (Figure 4.2). How do infants know how to map their parents' vocal labels to the correct parts of the environment amid myriad potential referents? Baldwin (1995) suggested that they use RJA and use the direction of their parent's gaze to guide them to the correct area of the environment, thereby reducing referential mapping errors. Infants' use of IJA also reduces the chance of referential mapping errors. IJA serves to denote something of immediate interest to the child. This allows parents to follow their child's attention to provide new information in a context when the child's interest and attention is optimal for learning (Tomasello & Farrar, 1986). Hence, joint attention may be conceived of as a self-organizing system that facilitates information processing in support of social learning (Mundy, 2003). This learning function is fundamental to the nature of joint attention as a milestone of early development (Bruner, 1975). Moreover, joint attention continues to operate throughout our lives in many ways, such as affecting our emotional responses to stimuli (Bayliss et al., 2006), facilitating math learning (Nathan, Eilam, & Kim, 2007), improving mental spatial rotation in adults (Böckler, Knoblich, & Sebanz, 2011), affecting recognition memory in adults (Kim & Mundy, 2012), and facilitating or changing stimulus processing (Frischen et al., 2007). Indeed, it is safe to say that without the

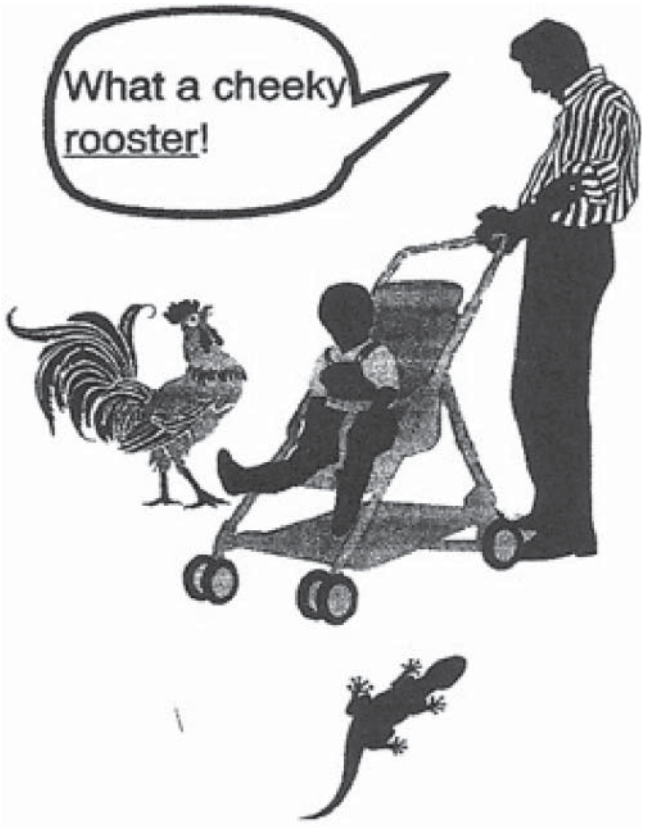


Figure 4.2 Illustration depicting the referential mapping problem encountered by infants in incidental social word learning situations. *Source:* D. Baldwin, Understanding the link between joint attention and language, in C. Moore & P. Dunham (Eds.), *Joint attention: Its origins and role in development* (pp. 131–158), Hillsdale, NJ: Erlbaum, 1995.

capacity for joint attention, success in many pedagogical contexts would be difficult. Imagine the school readiness problems of a 5-year-old who enters kindergarten, but is not facile with coordinating attention with the teacher. Similarly, children, adolescents, and adults who cannot follow, initiate, or join with the rapid-fire exchanges of shared attention in social interactions may be impaired in any social-learning context, as well as in their very capacity for relatedness and relationships (Mundy & Sigman, 2006).

To the degree that joint attention helps self-organize social learning in infancy, the more that children engage in joint attention, the more optimal social-learning opportunities they will help create for themselves. This may help to explain why the frequency with which infants engage in joint attention is positively related to their language acquisition and childhood IQ status (e.g., Mundy et al., 2007; Smith & Ulvund, 2003). More direct evidence of the links between joint attention and early learning is provided by the observation that coordinated social attention to pictures elicits electrophysiological evidence of enhanced neural activity and recognition memory associated with greater depth of processing in 9-month-olds (Kopp & Lindenberger, 2011; Striano, Chen, Cleveland, & Bradshaw, 2006a; Striano, Reid, & Hoel, 2006b).

Joint Attention and the Social-Cognitive Hypothesis

During the time that joint attention was first being conceptualized, another relevant kind of translational cognitive research was beginning to emerge. Premack and Woodruff (1978) described observational methods that enabled them to evaluate whether primates were aware of the thoughts or intention of conspecifics. That is, they began to study if apes had a theory of mind (ToM). Wimmer and Perner (1983), in the United Kingdom, further operationalized the construct of theory of mind with the development of the false belief task. With this paradigm they began to study the course of development of ToM and social cognition in preschool- and elementary school-age children.

Theory had previously linked the development of joint attention to the emergence of social cognition (Bretherton, 1991). This was further extended to its logical conclusion; namely, that young children would only consistently respond to or initiate joint attention bids if they understood that other people exerted intentional (goal-directed) control over their attention (Tomasello & Call, 1997). There was a cardinal problem with this model. Specifically, developmental studies indicated that infants displayed a wide range of individual differences in the frequency of their joint attention bids. For example, a large sample study indicated that 9-month-old infants displayed between four and forty IJA bids in a 20-minute interaction with an unfamiliar tester (Mundy et al., 2007). This variance was meaningful, in that the individual differences in IJA were reliable from 9 to 18 months of age (Figure 4.3). The social cognitive model was not developed to account for individual differences. Rather, it was an attempt to explain an all or none phenomenon, such as why older but not younger children display joint attention, or why typical children but not children with developmental disabilities display joint attention. However, joint attention does not simply develop in an all or none fashion. Some infants and children, with and without ASD, engage in more joint attention than others (e.g., Mundy, Sigman, & Kasari, 1990). It is very difficult to explain individual differences in joint attention on the order of those displayed in Figure 4.3 in terms of some scheme of incremental differences in understanding intentionality in others, at least as far as the social cognitive model has been articulated to date.

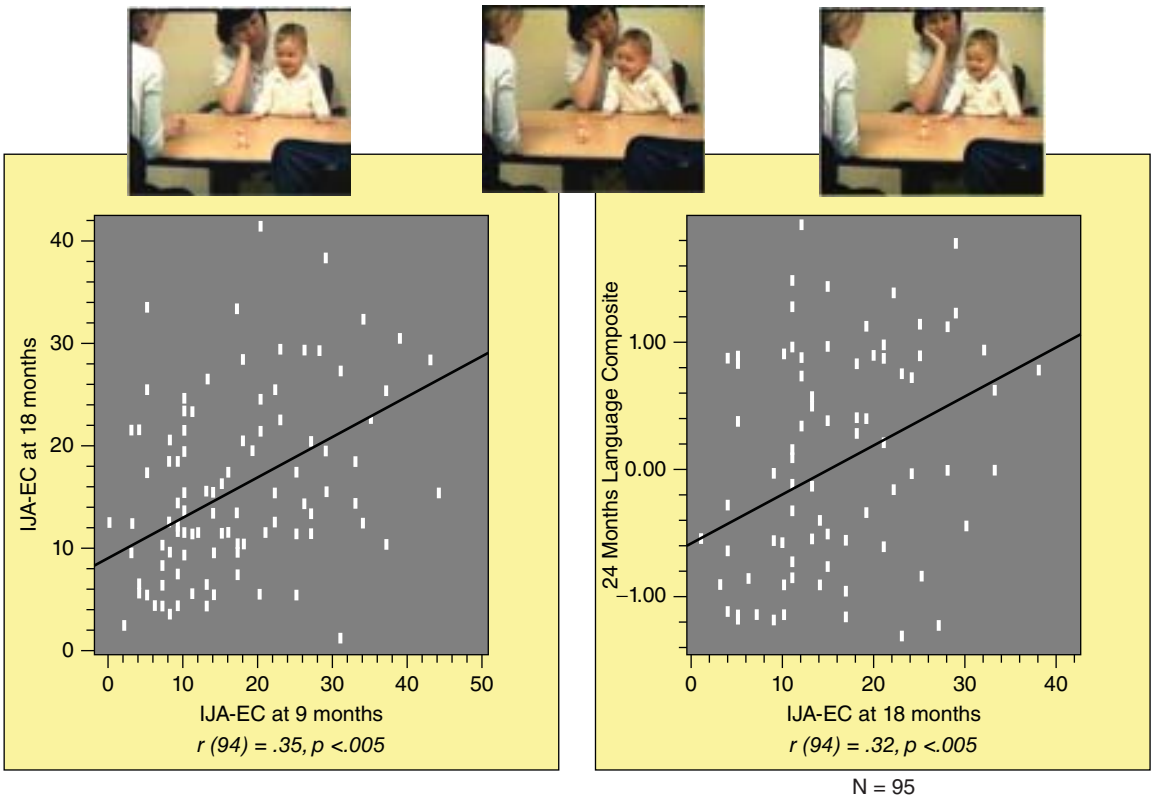


Figure 4.3 Illustration of the range and stability of individual differences in IJA alternating eye contact in 95 infants between 9 and 18 months of age (left panel), and the meaningful nature of individual differences in IJA alternating eye contact for a combined measure of receptive and expressive vocabulary development at 24 months. See footnote 1. *Source:* Data illustrations from P. Mundy, J. Block, A. Vaughan Van Hecke, C. Delgado, M. Venezia Parlade, & Y. Pomares, Individual differences and the development of infant joint attention, *Child Development, 78,* 938–954, 2007.

In summary, infant translational research provided a foundation for understanding the importance of joint attention for human development. Joint attention, by reflecting the capacity to share experiences and connect with others, likely provides a foundation for relational experiences with other people across the lifespan. Joint attention also provides a foundation for co-occurring and subsequent developments in language, thinking about others' minds, social learning, and social-emotional competence. It is not surprising, then, that the next major area of inquiry to develop would address better understanding the *neural foundations* of joint attention and its associated social-emotional outcomes.

THE NEURAL SYSTEMS OF JOINT ATTENTION

The neural systems associated with IJA and RJA development may be best understood within the context provided by two primary hypotheses within the contemporary research on functional brain architecture. The first hypothesis is that human cognition is best characterized as an emergent property of interactions among distributed, functionally specialized brain networks (McIntosh, 2000; Ramnani, Behrens, Penny, & Matthews, 2004). The second hypothesis is that there are at least *three superordinate brain networks* that interact in the development of cognition. These include the default network, which supports internal or self-referenced cognition, the dorsal attention system that serves external and other-referenced cognition, and the frontoparietal control or executive network, which regulates the expression or integration of the default and dorsal attention networks in cognition (Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013; Figure 4.4). The default and dorsal attention systems show little evidence of positive (interactive) connectivity and may conflict or inhibit functions of the opposing network. Alternatively, the frontoparietal network has positive connectivity with both the default and dorsal attention networks. Moreover, Spreng et al. (2013) identified three different types of

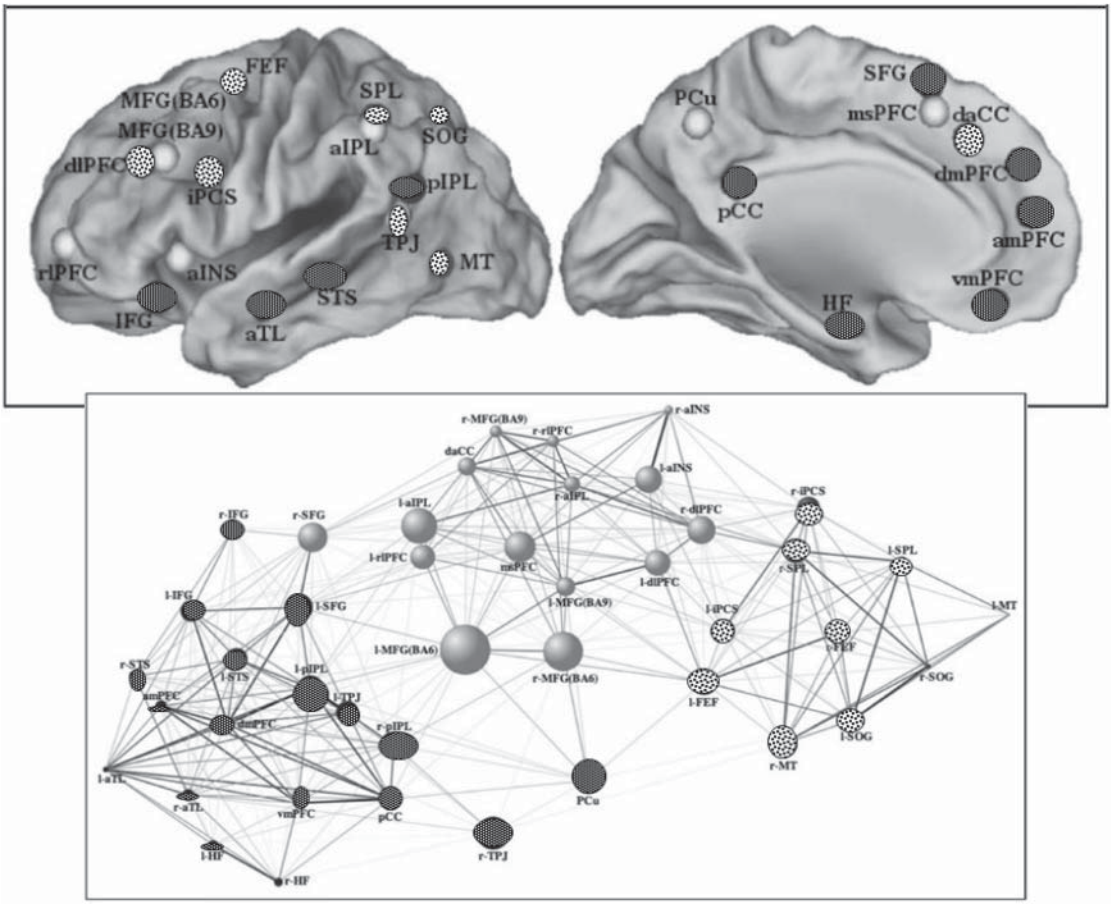


Figure 4.4 Illustration of the default network (circles with black background and white dots), frontoparietal network (circles in grayscale), and the dorsal attention network (circles with white background and black dots) in the top panel, and connectivity within and across networks in the bottom panel. *Source:* From R. N. Spreng, J. Sepulcre, G. R. Turner, W. D. Stevens, & D. L. Schacter, Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain, *Journal of Cognitive Neuroscience, 25*(1), 77, 80, 2013.

nodes within the frontoparietal network: default network aligned nodes, dorsal network aligned nodes, and dual aligned nodes. These nodes are thought to play a dynamic gatekeeping role in goal-directed cognition, mediating the adaptive balance between internal and external cognition, from moment to moment, across tasks and contexts. Regarding the development of these networks, Spreng et al. (2013, p. 82) noted, "Evidence suggests that patterns of intrinsic connectivity are sculpted by a history of repeated task-driven co-activation of brain regions, which in turn facilitates efficient coupling within task-relevant networks during future task performance." In other words, experience-based co-activity sculpts connectivity over time, which in turn affects later capacities (Cicchetti & Toth, 2009; Greenough, Black, & Wallace, 1987).

Early research on the similar and different processes that contribute to IJA and RJA emphasized the role of the dorsal attention network (Mundy, 2003). The dorsal attention network involves an anterior (frontal) and a posterior (temporal/parietal) component (Posner & Rothbart, 2007). Early studies suggested that IJA was more associated with the anterior attention network (Caplan et al., 1993; Henderson, Yoder, Yale, & McDuffie, 2002; Mundy et al., 2000; Torkildsen, Thormodsen, Syvensen, Smith, & Lingren, 2008), while RJA and related gaze-following behaviors were more closely associated with the posterior attention network (e.g., Emery, 2000; Frischen, Bayliss, & Tipper, 2007; Materna, Dicke, & Thern, 2008; Mundy et al., 2000). Interestingly, this observation provided one explanation of why higher primates (apes) were capable of RJA but not IJA (Tomasello, 2008). Several research groups have reported observations that suggest that the functions of the posterior network that support RJA are common to many primates, but the anterior network that

supports IJA is not well represented in primates other than humans (Astafiev, Shulman, Stanley, Snyder, Essen, & Corbetta, 2003; Emery, 2000; Gilbert & Burgess, 2008; Jellema, Baker, Wicker, & Perrett, 2000).

The posterior dorsal attention network regulates relatively involuntary attention, begins to develop in the first 3 months of life, and prioritizes orienting to biologically meaningful stimuli. It is supported by neural networks of the parietal/precuneus and superior temporal cortices (Figure 4.5). These neural networks are active in the perception of the eye and head orientations of others, as well as the perception of spatial relations between self, other, and the environment. The posterior system is especially involved in control of orienting on a trial-by-trial basis and the development of cognitive representations about the world built from information acquired through external senses (Cavanna & Trimble, 2006; Dosenbach et al., 2007; Fuster, 2006). This characterization of the posterior attention system comports with the notion that RJA is a relatively involuntary or reflexive response to human gaze shifts (Frischen et al., 2007).

In contrast, initiating joint attention was thought to be supported by later developments of the anterior dorsal attention network which were involved in cognitive processing addressing volitional, self-initiated, goal-directed action (Mundy, 2003). This network includes the anterior cingulate, rostral medial superior frontal cortex (including the frontal eye fields), anterior prefrontal cortex, and orbital frontal cortex (e.g., Dosenbach et al., 2007; Fuster, 2006). The development of the intentional control of visual attention is thought to begin at about 3 to 4 months of age. At that time, a pathway from the frontal eye fields (BA 8/9) begins to release the superior colliculus from inhibition, which enables the development of active prospective control of saccades and visual attention (Canfield & Kirkham, 2001; Johnson, 1990). The function of this pathway may underlie 4-month-old infants' ability to suppress automatic visual saccades to respond to a second, more attractive stimulus (Johnson, 1995), and 6-month-olds' ability to respond to a peripheral target when central, competing stimuli are present (Atkinson, Hood, Wattam-Bell, & Braddick, 1992). Hypothetically, the functions of this pathway also enable intentional gaze alternation between interesting events and social partners (Mundy, 2003).

More recent research suggests that it may not be accurate to allocate IJA exclusively to anterior systems functions and RJA to posterior system functions. Indeed, reliance only on the dorsal attention network is likely insufficient to characterize the complete system of neural networks that are involved in the maturation of human joint attention. For example, Schilbach et al. (2010) used imaging (fMRI) to examine whether the cortical correlates of RJA and IJA were common or distinct in adults. This research group reported that joint attention elicited activation in a specific frontal-temporal-parietal distributed network, that likely contains elements of the default and

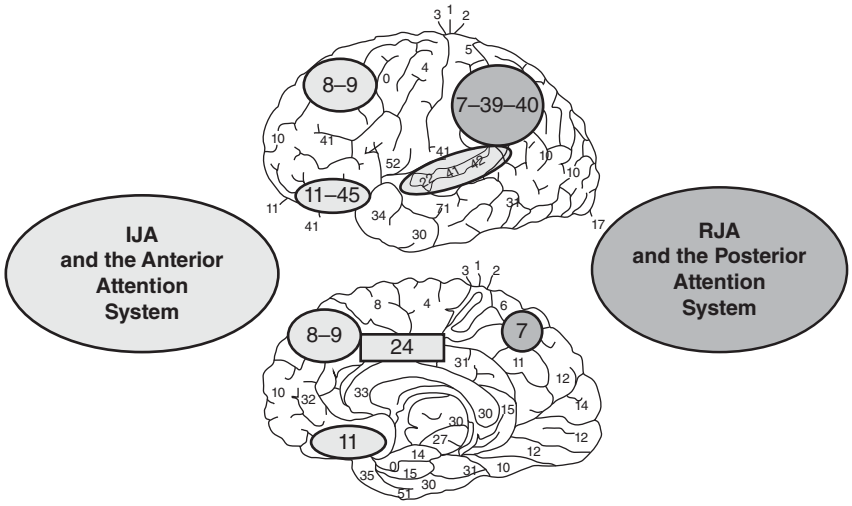


Figure 4.5 Illustration depicting the lateral (top) and medial (bottom) illustrations of Brodmann's cytoarchitectonic areas of the cerebral cortex associated with initiating joint attention and the anterior attention system, as well as RJA and the posterior attention systems. The former include areas 8 (frontal eye fields), 9 (prefrontal association cortex), 24 (anterior cingulate), 11, and 47 (orbital prefrontal association cortex). The latter include areas 7 (precuneus, posterior parietal association area), 22, 41, and 42 (superior temporal cortex), and 39 and 40 (parietal, temporal, occipital association cortex). *Source:* Illustration from P. Mundy & L. Newell, Attention, joint attention and social cognition, *Current Directions in Psychological Science*, *16*, p. 271, 2007.

frontoparietal network, as well as the dorsal attention network. Moreover, Schilbach et al. (2010) observed that RJA, but not IJA, was uniquely associated with medial frontal gyrus activation, a region that is part of the frontoparietal control network in the Spreng et al. (2013) model. Consistent with this observation, recent behavioral development studies also suggest that executive cognitive control functions are associated with RJA in infancy (Vaughan Van Hecke et al., 2012). In contrast, Schilbach et al. (2010) observed that IJA was more exclusively associated with striatal cortex activation than was RJA. Striatal cortex is associated with reward processing that is instrumental to motivating self-initiated goal directed behavior. This observation is consistent with the notion that prosocial motivation likely plays a role in IJA development (Vaughan Van Hecke et al., 2007). The ventral striatum is not represented in the Spreng et al. (2013) model, however; it is part of a reward-processing network that involves elements of the Default Network described by Spreng and colleagues, such as the dorsal medial prefrontal cortex (mPFC) (Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011).

Subsequently, Redcay et al. (2012) reported a seminal sequence of fMRI observations on joint attention with adults. In this study, both IJA and RJA were associated with the activation of the posterior superior temporal sulcus and the mPFC, which are components of the default network (Spreng et al., 2013) often associated with social cognition. IJA displayed relatively stronger association with activation in the middle frontal gyrus and parietal cortex, areas associated with the dorsal attention and frontoparietal control networks described by Spreng et al. (2013). Alternatively, RJA was uniquely associated with ventral medial frontal and occipital cortical activation in this study. Only the former is included in the Spreng model and is aligned with the default network. Perhaps most interesting of all, Redcay et al. (2012) provided the only connectivity analysis to date and found evidence that joint attention is associated with functional connectivity among nodes that are part of all three networks described by Spreng et al. (2013).

Of course, the neurofunctional organization observed in adults may not necessarily inform our understanding of the developmental systems that give rise to the early development of joint attention. However, studies indicate that many elements of a distributed joint attention network that are evident in research with adults are also evident in early developmental research with infants. Grossman and Johnson (2009) reported that a pattern of anterior (medial frontal, left ventral frontal) and posterior (right temporal/parietal) cortical activation is associated with response to joint attention in 5-month-olds. Elison et al. (2013) also reported that the relative functioning of anterior frontal white matter fiber tracts (uncinate fasciculi) and posterior temporal white matter fiber tracts (inferior longitudinal fasciculi) at 6 months of age predicts RJA development at 9 months of age. It is also the case that a pattern of EEG activation across a distributed anterior and posterior cortical system predicts IJA development in infants from 14 to 16 months of age (Henderson et al., 2002).

Thus, the current research literature has given rise to the parallel and distributed processing model (PDPM) of joint attention development and its impairment in ASD (Mundy et al., 2009). According to this model, initial executive and behavioral motivation biases promote the tendency of infants to engage in the practice of processing of internal information about the direction and focus of their own visual attention, while also processing external information about the visual attention of other people. This dynamic system of early self-other information processing about attention leads to the concretization of connections between an anterior and posterior neurocognitive network that supports fast and efficient human joint attention (Figure 4.6; Mundy & Newell, 2007). This model incorporates the notion that patterns of what may appear to be intrinsic connectivity in adults have been sculpted by a history of repeated (practiced) task-driven co-activation of brain regions during development (Cicchetti & Toth, 2009; Spreng et al., 2013). The model is also consistent with neurocognitive theory that claims that an emergent function of the human rostral-medial frontal cortex is the capacity to switch attention between self-generated information and perceptual (external) information in support of social cognition (Gilbert & Burgess, 2008). The PDPM suggests that this function is allocated to the rostral medial frontal cortex, in large part, as a function of the adequate bio-behavioral exercise of joint attention behaviors early in development. Moreover, if behavioral practice does not facilitate efficient couplings within task-relevant networks, then the joint attention system may display quantitative reductions in its rapid and efficient execution. This in turn results in increased cognitive load associated with joint attention engagement and consequent reduced effectiveness of cognitive processing within social interactions, such as social learning situation or social conversational discourse (Mundy & Jarrold, 2010; Mundy et al., 2009, 2010).

Recently, two studies have provided evidence that part of the development of joint attention early in life may be characterized by an increase in the speed or efficiency with

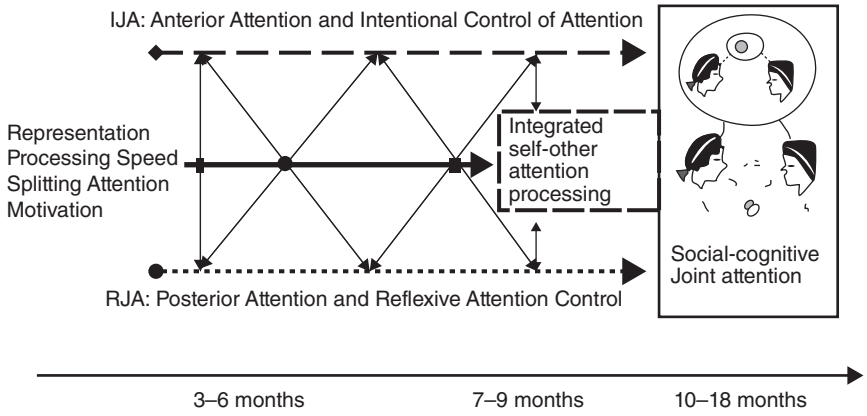


Figure 4.6 An illustration of the parallel distributed information processing system model of joint attention and social cognition. In this model, different types of lines depict the multiple paths of joint attention development. The posterior attention system path associated with RJA development is illustrated with a dotted line ····▶ and the anterior attention system path associated with IJA development is illustrated with a dashed line – – –▶. The central solid line in the figure depicts the developments of other processes during infancy that influence joint attention development, such as representational ability, speed of processing, motivation, and executive attention control, as well as each other, during infancy. The diagonal arrows connect all paths throughout early development. This reflects the dynamic and coactive nature of joint attention development, whereby the maturation of attention, cognitive, and affective systems interact in reciprocal cause and effect relations with experience, including the experiences children create for themselves through their own actions. Finally, the development of integrated self and other attention processing is considered to be a social attention executive function of the anterior system that emerges in the 4- to 9-month period. This is represented by the box. The capacity to integrate and share overt aspects of attention provides a foundation for the ability to share covert aspects of attention, such as representations, and social cognition. *Source:* From P. Mundy & L. Newell, Attention, joint attention and social cognition, *Current Directions in Psychological Science*, *16*, p. 272, 2007.

which young children execute joint attention behaviors. Gredebäck, Fikke, and Melinder (2010) reported longitudinal data across assessments at 2, 4, 6, and 8 months of age, whereupon infants displayed a significant linear increase from age to age in the tendency to shift gaze in response to the line of regard of a tester. More pertinent, though, was the observation that infants displayed a significant linear decrease in their latency to follow gaze, from about 3.5 seconds at 2 months to 1.5 seconds at 8 months. We have observed a similar longitudinal decrease in RJA latency, from approximately 2 seconds at 9 months to 0.8 seconds at 18 months (Vaughan Van Hecke et al., 2012). Moreover, 9-month-olds displayed a reduction in latency with practice across four RJA trials (Figure 4.7).

A definitive interpretation of the causes of the decrease in latency in RJA in these studies is not yet possible. Nevertheless, these patterns of results are consistent with the notion that execution of joint attention behaviors becomes more rapid, efficient and, perhaps, automated, across the first two years of life in typical development. One possibility is that this is due to practice effects interacting with interconnectivity within the frontal and posterior joint attention network that has been observed to develop in the first years of life (Elison et al., 2013).

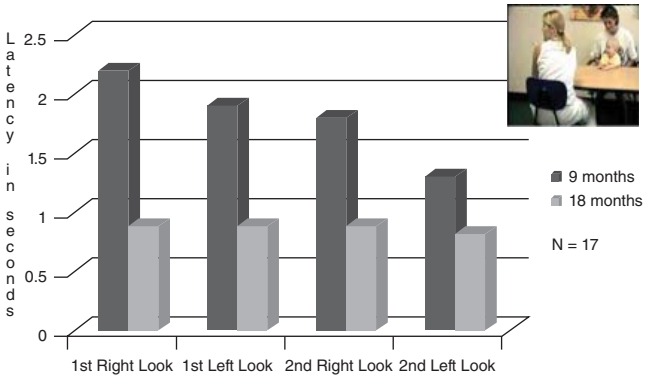


Figure 4.7 An illustration of the decrease in response latency to left and right RJA trials on the Early Social-Communication Scales (Mundy, Hogan, & Doehring, 1996) between 9 and 18 months of age. Also illustrated is the decrease in response latency across a sequence of RJA trials exhibited by infants at 9 months of age. See footnote 1.

In summary, the PDPM model of joint attention holds that integrated and, at times, collaborative processing of information about one's own focus of attention and the attention of other people is a necessary faculty for competent human social engagement, social learning, and social communication. In addition, joint attention is a

form of parallel processing that occurs across a distributed cortical network. Practice with joint attention in infancy contributes to the development of an efficient distributed neural network that plays a crucial role in human social cognition. The potential role of parallel and distributed processing in synthesis in human social cognition has previously been recognized (Decety & Sommerville, 2003; Keysers & Perrett, 2004). However, the developmentally primary role of joint attention in this synthesis is less well recognized.

Social Cognition and the PDPM of Joint Attention

Social-cognitive models often describe joint attention in terms of incremental stages of knowledge about the intentionality of other people. Baron-Cohen (1995) described a sequence of cognitive modules that included the *intentionality detector* (ID; i.e., a dedicated cognitive facility that attributes goal directed behavior to objects or people) and the *eye direction detector* (EDD; i.e., senses and processes information about eyes). These combine to form the *shared attention mechanism* (SAM), a cognitive module that represents self and other as attending to the same referent and attributes volitional states (intentionality) to direction of gaze of other people. As infancy ebbs the *theory of mind mechanism* replaces SAM and enables representation of the full range of mental states of others and enables us to make sense of others' behaviors.

Tomasello et al. (2005) more explicitly described joint attention development in terms of three stages of what infants know about other people. In the *understanding animate action stage*, 3- to 8-month-old infants can perceive contingencies between their own animate actions and emotions relative to the animate actions and affect of others. However, they cannot represent the internal mental goals of others that are associated with these actions. Next, in the *understanding of pursuit of goals* stage, 9-month-olds become capable of shared action and attention on objects (e.g., building a block tower with parents).

Tomasello et al. (2005) suggested that the *understanding of pursuit of goals* stage involves joint perception, rather than joint attention, because the social-cognitive capacity to represent others' internal mental representations necessary for true joint attention is not yet available. However, this ability emerges between 12 and 15 months in the *understanding choice of plans* stage. This stage is heralded when infants become truly active in initiating episodes of joint engagement by alternating their eye contact between interesting sights and caregivers (Tomasello et al., 2005). This shift to active alternating gaze indicates infants' appreciation that others make mental choices about alternative actions that affect their attention. Infants also now know themselves as agents that initiate collaborative activity based on their own goals. Hence, the development of true joint attention at this stage is revealed in the capacity to adopt two perspectives analogous to speaker–listener.

The capacity to adopt two perspectives is also assumed to be an intrinsic characteristic of symbolic representations. In this regard, Tomasello et al. (2005) raised a truly seminal hypothesis, that symbolic thought is a developmental transformation of joint attention. They argue that symbols themselves serve to socially coordinate attention so that the intentions of the listener align with those of the speaker. In other words, linguistic symbols both lead to and are dependent upon the efficient social coordination of covert mental attention to common abstract representations among people. This hypothesis fits well with the parallel and distributed processing model of joint attention, but the PDPM places it in a substantially different developmental framework.

The PDPM does not emphasize functional segregation of cognitive systems implicit to modular perspectives, but instead emphasizes the cortically multi-determined nature of human cognition because of the "massively parallel nature of human brain networks and the fact that function also emerges from the flow of information between brain areas" (Ramnani et al., 2004, p. 613). Furthermore, cognitive development need not be construed only in terms of changes in discontinuous stage knowledge. It can also be modeled as a continuous change in the speed, efficiency, and combinations of information processing that give rise to knowledge (Hunt, 1999). Specifically, the PDPM envisions joint attention development in terms of increased speed, efficiency, and complexity of processing of (1) internal information about self–referenced visual attention, (2) external information about the visual attention of other people, and (3) the neural networks that integrate processing of self-generated visual attention information with processing of information about the visual attention behavior of other people (Mundy & Newell, 2007).

Consequently, the notion that *true* joint attention does not emerge until requisite social-cognitive knowledge emerges at 12–15 months (Tomasello et al., 2005) is not germane to the PDPM. Rather, consistent with a growing empirical literature, the PDPM holds that the true joint processing of attention information begins to be practiced by infants by 3 to 4 months of age (D'Entremont, Hains, & Muir, 1997; Farroni, Massuccessi, & Francesca, 2002; Hood, Willen, & Driver, 1998, Morales et al., 1998; Striano, Reid, & Hoel, 2006b; Striano & Stahl, 2005). Indeed,

even the types of active alternating gaze behaviors thought to mark the onset of true joint at 12–15 months (Tomasello et al., 2005) develop no later than at 8–9 months of life, and quite possibly earlier (Mundy et al., 2007; Venezia et al., 2004).

Equally important, the PDPM assumes that joint attention is not replaced by the subsequent development of social-cognitive processes. Instead, joint attention is thought to remain an active system of information processing that supports cognition through adulthood (Mundy & Newell, 2007). As an example, recall the hypothesis that linguistic symbols enable the social coordination of covert attention to common mental representations across people (Tomasello et al., 2005). According to the PDPM, symbolic thinking involves joint attention but does not replace joint attention. Just as 12-month-olds can shift eye contact or use pointing to establish a common visual point of reference with other people, 4-year-olds can use symbols to establish a common reference to covert mental representations with other people. Symbolic representations are often, if not always, initially encoded during the joint processing of information about the overt attention of self and of others directed toward some third object or event (Adamson, Bakeman, & Dekner, 2004; Baldwin, 1995; Werner & Kaplan, 1963). The PDPM combines that hypothesis with the connectionist notion that "representations can take the form of patterns of activity distributed across processing units" that occurred during encoding (Munakata & McClelland, 2003, p. 415). Together these two ideas lead to the assumption of the PDPM that symbol acquisition incorporates the distributed activation of the joint self-attention and other-attention neural processing units, which were engaged during encoding, as part of their functional neural representational mappings. Hence, the distributed joint attention processing system may always be activated as a network encoding that contributes to the intersubjectivity (i.e., shared attention and meaning) of symbolic thought.

In infancy, the distributed joint attention processing system is initially effortful. However, thousands of episodes of practice allow the joint information processing of self–other attention to become efficient, less effortful, and even automatically activated in social engagement. As this occurs, joint attention becomes a social-executive subroutine that runs in support of symbolic thought, as well as that capacity to maintain a shared focus in social interactions and in social cognition (Mundy, 2003). The distributed neural activation patterns associated with joint attention are part of infants' sense of developing sense of relatedness to others (Mundy & Hogan, 1994; Mundy, Kasari & Sigman, 1992). Moreover, the distributed neural activation associated with joint attention can be thought of as an enduring stratum of a more continuous spiral of human social-neurocognitive development that supports, if not enables, later emerging human symbolic, linguistic, and social cognitive facilities (Figure 4.8).

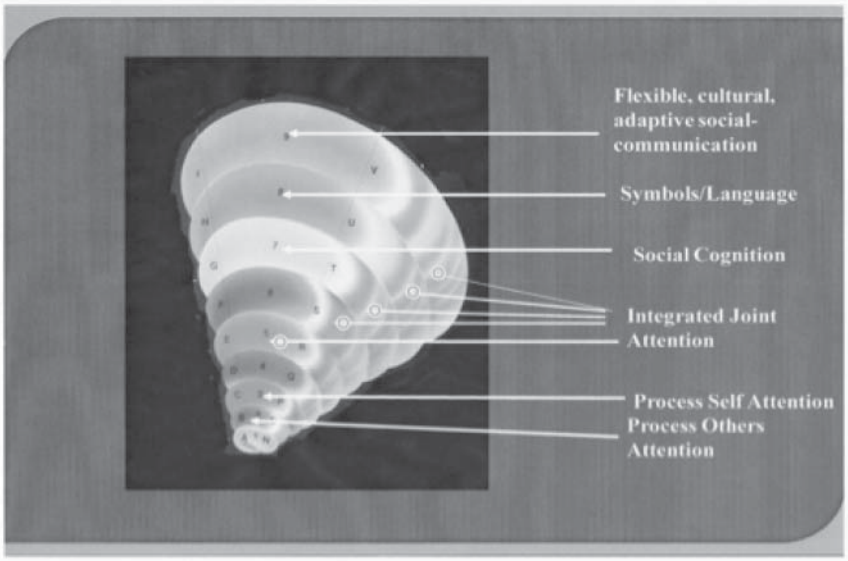


Figure 4.8 An illustration of the continuous information processing model of social attention, joint attention, and social-cognition. Here development is modeled as a spiral, in which the initial acquisition of the capacity for integrated processing of information about self- and other- attention (joint attention) remains an active but deeper layer of cognitive activity throughout life that supports symbolic thought, language, and cultural social exchange.

Inside-Out Processing and the Joint Attention PDPM

In addition to parallel and distributed processing, the PDPM may be distinguished from other models by its constructivist perspective on development. Rather than focusing on the development of knowledge about others, the PDPM gives equal footing to the significance of infants' development of their own intentional visual behavior in joint attention and social cognitive development (Mundy et al., 1993). The assumption here is that neonates and young infants receive greater quantities and fidelity of information about self-intended actions (e.g. active looking) through proprioception than they receive about other's intended actions through exteroceptive information processing. Thus, infants have the opportunity to learn as much or more about intentionality from their own actions as from observing the actions of others. A corollary of this assumption of the PDPM is that joint attention is an embodied form of cognition (Feldman & Narayanan, 2004). Its development is a constructivist process that involves self-perception as a foundation for the attribution of meaning to the perception of others' behaviors. We have referred to this as the inside-out processing assumption of the PDPM (Mundy & Vaughan Van Hecke, 2008).

The general tenor of this constructivist assumption is nothing new. Bates et al. (1979) suggested that a sense of self-agency was basic to joint attention. More generally, Piaget (1952) argued that infants do not learn through the passive perception of objects (or others) in the world. Rather, infants take action on objects and learn from their (causal) actions. They then modify their actions, observe changes in causal relations, and learn new things about the physical world. Thus, Piaget viewed the processing of self-initiated actions on objects as a singularly important fuel for the engines of cognitive development. The constructivist viewpoint is not only central to the PDPM, but it is also a mainstay of contemporary connectionist biological principles of typical and atypical neurocognitive development (e.g., Blakemore & Frith, 2003; Elman, 2005; Mareschal et al., 2007; Meltzoff, 2007; Quartz, 1999).

The vast number of functional neural connections that are made in early postnatal brain development are thought to be too numerous to be specified by genes alone. Instead, genes specify relatively wide channels of potential neurodevelopmental architecture (e.g., Quartz, 1999). Within these prescribed channels, the specifics of important functional connections in the developing nervous systems are sculpted by our experience. Since most of us experience relatively similar environments and experiences in early developmental life, brain organization displays significant similarities across most people (Mareschal et al., 2007). Greenough et al. (1987) referred to this gene–environment interaction in the ontogeny of neural connections as experience–expectant neurodevelopment. They also explicitly noted that infants' generation of actions, and observations of social reactions, likely play a role in experience-expectant processes specific to the neurodevelopmental basis of human social behavior (Cicchetti & Toth, 2009). So, just as Piaget envisioned that infants learn about the physical world from their self-generated actions on objects, it is reasonable to think that a significant portion of what infants learn about the social world comes from their self-generated actions with people. One type of self-generated action that may be developmentally key in this regard is active vision.

Active Vision and the Joint Attention PDPM

One of the first and most vitally informative types of actions infants take involves the self-control of their looking behaviors, or active vision. The science of vision has moved away from the study of seeing or passive visual perception to the study of looking or intentional, active vision and attention deployment (Findlay & Gilchrist, 2003). Active vision in infancy begins to develop at 3–4 months of age (e.g., Canfield & Kirkham, 2001; Johnson, 1990, 1995). It involves the goal-directed selection of information to process and can elicit contingent social behavior responses from other people, such as parental smiles, vocalizations, or gaze shifts. It also is one of the first types of volitional actions that infants use to control stimulation to self-regulate arousal and affect (Posner & Rothbart, 2007).

Vision and looking behavior have unique properties. Vision provides information regarding the relative spatial location of oneself and other people. Moreover, direction of gaze conveys the distal and proximal spatial direction of our attention to others, and vice versa. Comparable information on the spatial direction of attention is not as clearly available from the other senses. This is especially true in the first 9 months of life and for distal information. The importance of spatial visual information for the development of joint attention was emphasized by Butterworth and Jarrett (1991) in their influential article "What Minds Have in Common Is Space."

In some sense, primate eyes are specialized for *social* spatial attention processing (e.g., Tomasello, Hare, Lehman, & Call, 2006). Frontal binocular eye positions allow for

enhanced spatial processing and depth of perception through parallax perception. Intricate musculatures allow for rapid visual focus on objects that are far or near. Equally important, precise information about the spatial direction of attention is available from human eyes because of the highlighted contrast between the dark coloration of the pupil and iris, versus the light to white coloration of the sclera. These observations have led to the suggestion that the ease of processing the direction of attention of other people's eyes contributed to the human phylogenetic and ontogenetic development of social cognition (e.g., Tomasello et al., 2006).

It is also the case, though, that these characteristics of the human eye allow the saccades of infants to be readily observed by other people. Consequently, infant saccades can effectively act as elicitors of contingent social feedback. When infants shift attention to an object, their parents may pick-up and show them the object. When infants shift attention to their parents' eyes, they may also receive a vocal, affective, or physical parental response. Thus, just as the characteristics of eyes make it easier for infants to perceive the attention of others, the signal value of eyes makes the active control of vision a likely nexus of infants' developing sense of agency. A corollary here is that a sense of visual self-agency may play a role in joint attention and social-cognitive development.

The notion that active vision has primacy in social development relates back to the time-honored observation that visual behavior is at least as important to human social development as physical contact (Rheingold, 1966; Robson, 1967). However, the contemporary literature on social-cognitive development emphasizes only the importance of the information infants gather from processing the visual attention of others (e.g., Johnson et al., 2005). It neglects the potential importance of the information infants process about their own active vision, and socially contingent responses.

Alternatively, the active vision assumption of the PDPM offers one plausible explanation for why activation of the frontal eye-fields (a cortical area involved in volitional saccadic control) is a consistent significant correlate of social-cognition in imaging studies (Mundy, 2003). This is because the volitional control of active vision, via the frontal eye fields, may be central to developing an integrated sense of the relations between self-attention and other-attention, which is fundamental to joint attention and subsequent social cognition. This hypothesis leads to the testable prediction that the frontal eye fields should be less active in social-cognitive processing in older congenitally blind individuals than in sighted individuals (Mundy & Newell, 2007). If true, this hypothesis may also help to explain some of the developmental commonalities observed for children with autism and blind infants (Bigelow, 2003; Hobson, Lee, & Brown, 1999).

DYNAMIC SYSTEMS AND THE JOINT ATTENTION PDPM

The PDPM emphasizes inside-out processing, constructivism, and the role of active vision in the development of joint attention. However, it does not maintain that the inside-out processing of self-attention is more important for social-cognitive development than outside-in processing of others' attention. This is because the PDPM holds that social meaning, and even conscious self-awareness, cannot be derived from processing either self-attention or others' attention in isolation (cf. Decety & Sommerville, 2003; Keysers & Perret, 2004; Vygotsky, 1962). Ontogeny may be best viewed as a dynamic system that, through interactions of multiple factors over time and experience, coalesce into higher order integrations, structures, and skills (e.g., Smith & Thelen, 2003). The development of joint attention, or the joint processing of the attention of self and other, is such a dynamic system. Indeed, the pertinence of joint attention for human development derives in no small part from the unique synthesis that arises from the rapid, parallel processing of self-attention and other-attention across distributed neural networks. Consequently, it is not possible to account for the role of joint attention in typical or atypical development with research or theory that focuses on only one of its elements in isolation.

The dynamic system of joint attention begins to synergize as frontal executive functions increasingly enable attending to multiple sources of information during infancy. According to one definition, executive functions involve the transmission of bias signals throughout neural networks to selectively inhibit comparatively automatic behavioral responses, in favor of more volitional, planned, and goal-directed ideation and action, in problem-solving contexts (Miller & Cohen, 2001). These bias signals act as regulators for the brain, affecting visual processes and attention, as well as other sensory modalities and systems responsible for task-relevant response execution, memory retrieval, emotional evaluation, and so forth. The aggregate effect of these bias signals is to guide the flow of neural activity along pathways that establish the proper mappings between inputs, internal

states, and outputs needed to perform a given task more efficiently (Miller & Cohen, 2001). According to this definition, joint attention development may be thought of as reflecting the emergence of frontal bias signals that establish the proper mappings across (1) outside-in posterior cortical (temporal-precuneus) processing of inputs about the attention behaviors of other people; and (2) rostral-medial-frontal (BA 8–9, anterior cingulate) inside-out processing of internal states and outputs related to active vision. This mapping results in the integrated development of a distributed anterior and posterior cortical joint attention system.

It is conceivable that the early establishment of this mapping of the joint processing of attention is formative with respect to the shared neural network of representations of self and other, which Decety and Grezes (2006) suggested is essential to social cognition. It also may play a role in what Keysers and Perrett (2004) described as a Hebbian learning model of social cognition. Neural networks that are repeatedly active at the same time become associated, such that activity (e.g., representations) in one network triggers activity in the other (Hebb, 1949). Keysers and Perrett suggested that *common* activation of neural networks for processing self-generated information and information about conspecifics is fundamental to understanding the actions of others. This Hebbian learning process is fundamental to the hypothesized functions of simulation (Gordon, 1986) and mirror neurons (Decety & Sommerville, 2003; Williams, 2008) that are commonly invoked in current models of social-cognitive development.

The PDPM is consistent with these interrelated ideas and suggests that Hebbian mapping in social cognition begins with integrated rostral medial frontal processing of information about self-produced visual attention and posterior processing of the attention of others. Moreover, the PDPM specifically operationalizes the study of development of this dynamic mapping system, in terms of psychometrically sound measures of early joint attention development (Mundy et al., 2007). Indeed, IJA assessments may be relatively powerful in research on social cognitive development and developmental disorders because they measure variance in the whole dynamic system, rather than any one of its parts alone.

Once well practiced, the joint processing of attention information requires less mental effort. As the basic joint attention process is mastered and its effort to engage goes down, it can become integrated as an executive function that contributes to the initial development and increasing efficiency of social-cognitive problem solving. Thus, joint attention development may be envisioned as shifting from learning to do joint attention in the 6 to 9 months to learning from joint attention in the second year of life (Mundy & Vaughan Van Hecke, 2008; Figure 4.9). In the learning from phase, the capacity to attend to multiple sources of information in triadic attention deployment becomes more common (Scaife & Bruner, 1975). Triadic attention contexts provide infants with rich opportunities to compare information gleaned through processing internal states associated with volitional visual attention deployment and the processing of the visual attention of others in reference to a common third object or event. Through simulation (Gordon, 1986) infants may begin to impute that others have intentional control over their looking behavior that is similar to their own.

The role of simulation in the *learning-from phase* of joint attention development is well illustrated by a recent sequence of elegant experimental studies (Brooks & Meltzoff, 2002). Often, 12-month-olds follow the gaze direction of testers even if their eyes are closed. After 12 months, though, infants discriminate and follow the gaze of testers whose eyes are open but not closed. This suggests that infants' understanding of the meaning of the eye gaze of others may improve in this period, leading older infants to inhibit looking in the eyes-closed condition.

To examine this interpretation, Meltzoff and Brooks (2008) conducted an experimental intervention. They provided 12-month-olds with the experience of blindfolds that occluded their own looking behavior. After gaining that experience, 12-month-olds did not follow the head turn of blindfolded testers, but did follow the head turn and gaze of nonblindfolded testers. Meltzoff and Brooks also provided 18-month-olds with experience with blindfolds that looked opaque but were transparent when worn. After this condition, the 18-month-olds reverted to following the gaze of blindfolded social partners. These data strongly suggest that the infants demonstrated inside-out learning and constructed social-cognitive awareness about others' gaze based on the experience of effects of blindfolds on their own active vision.

In sum, infant translational research proposed that a foundational system of integrated attention to self and other, supported by a dynamic, distributed neural network, provides for enhancements in social communication, social learning, and social cognition in typical development. The ability to utilize this integrated, or joint, attention to share experiences with others develops in early infancy, and transitions from a phase of learning-to utilize joint attention to learning-from joint attention in toddlerhood, childhood, and even beyond. Individual differences in the capacity to utilize joint attention likely play a role in the range of

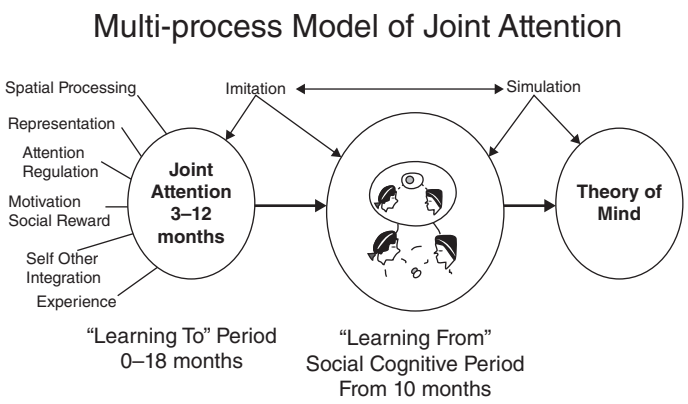


Figure 4.9 In the first year, the development of joint attention involves the "learning-to" phase. This period comprises the integration of executive, motivational, and imitative processes to support the routine, rapid, and efficient (error-free) execution of behavioral patterns, which enable infants' coordination of overt processing of aspects of visual self-attention, with processing of the social attention of other people. In the latter part of the first year and the second year, infants can better monitor their own experiences and integrate them with information about social partners during joint attention events. This provides a critical multimodal source of information to the infants about the convergence and divergence of self- and other-experience and behavior during sharing information in social interactions. Theoretically, this provides the stage for the "learning-from" phase of joint attention development. In this stage, infants can control their attention to self-organize and optimize information processing in social learning opportunities. The integration of anterior and posterior self–other attention processing (Figure 4.5) provides a neural network that enriches encoding in social learning. The internalization of the overt joint processing of attention to the covert joint processing of attention to representations is part of an executive system that facilitates symbolic development and the social cognition. Both symbolic thought and social cognition may be characterized by a transition from learning to socially coordinate overt attention to the capacity to socially coordinate covert mental representations of the attention of self and others.

social-emotional and social-cognitive skill present in the population. The next natural area of inquiry, then, involves how difficulties with joint attention play a cardinal role in a population in the extreme range of deficits in social abilities: individuals with ASD.

JOINT ATTENTION AND DEFINING THE SOCIAL DEFICITS OF ASD

The recognition of the centrality of joint attention impairment in the development of ASD followed from the growing understanding of how and when typical infants develop the ability to share experiences with other people (Bates et al., 1979; Bruner, 1975; Rheingold et al., 1976; Trevarthen, 1979; Werner & Kaplan, 1963). While other domains of social behavior, such as imitation, face processing, empathy, theory of mind, and pragmatic communication skills, are prominent in the literature (Travis & Sigman, 1998), none have had the impact on understanding the nature of ASD, its diagnosis, or its treatment that can be claimed for the study of joint attention (e.g., Bruinsma et al., 2004; Charman, 1997; Dawson et al., 2004; Kasari et al., 2006, 2008; Mundy & Crowson, 1997; Mundy et al., 2009; Sigman & Ruskin, 1999).

It was Frank Curcio (1978) who first documented joint attention disturbance in individuals with ASD. He noted that 50% of a sample of elementary school-age children with ASD observed in classrooms systematically used eye contact and conventional gestures to express their requests. However, few, if any, children with ASD displayed evidence of the use of eye contact or gestures to initiate joint attention bids or nonverbal declaratives. Curcio concluded that impairments in the capacity to initiate joint attention and declarative communicative functions could be central to the nature of the social impairments of ASD. Subsequent studies indicated that Curcio was correct (e.g., Charman, 2004; Dawson et al., 2004; Loveland & Landry, 1986; Mundy et al., 1986; Sigman & Ruskin, 1999; Wetherby & Prutting, 1984).

In work in the laboratory of Marian Sigman at UCLA, samples of children with ASD were compared with mental age, chronological age, and IQ-matched samples of 4- to 7-year-old children with intellectual disabilities and samples of mental age-matched children with typical development. These studies indicated that children with ASD displayed deficits in joint attention in interactions with unfamiliar testers (Mundy et al., 1986), as well as parents, compared with both control groups (Sigman et al., 1986). Moreover, just as Curcio observed, children with

ASD displayed quantities and qualities of communication bids to request objects and turn-taking opportunities with social partners that were comparable to those observed in the control sample with intellectual disabilities (ID). These case-controlled studies indicated that children with ASD did not display pervasive differences in eye contact or social-communication behaviors relative to children with ID, but rather a more nuanced pattern of syndrome-specific strengths and weaknesses in their social behaviors. They displayed comparable levels of eye contact in requesting and turn-taking social interactions. However, an eye contact disturbance specific to ASD was clearly manifested in their diminished use of alternating gaze to spontaneously initiate sharing of experience of a mechanical toy with the tester. This type of alternating gaze behavior is illustrated in Figure 4.1.

We cannot yet definitively describe why a child does or does not engage in IJA during a social interaction. Nevertheless, ESCS testers often arrived at the impression that IJA behaviors signal a child's desire (motivation) or goal (intent) to share the experience of an object or event, or spontaneously elicit attention to the child's own experience of an object or event (Figure 4.1). Hence, it was not too surprising to find that higher or lower frequencies of alternating eye contact in young children, with or without ASD, were significantly related to parents' independently assessed perceptions of their child's social relatedness (Mundy et al., 1994). These observations raised the possibility that diminished IJA was central to what Kanner perceived as the cardinal impairment in relatedness and positive affective contact with others in ASD (e.g., Mundy & Sigman, 1989).

The Social-Motivation Model and Joint Attention in ASD

The idea that IJA was related to a disturbance in positive social-affective contact in autism was more directly supported by research in the early 1990s that showed that about 60% of the IJA bids displayed by typical infants and children with intellectual disabilities involved the conveyance of positive affect (Kasari, Sigman, Mundy, & Yirmiya, 1990; Mundy, Kasari, & Sigman, 1992). However, positive affect was much less frequently part of the IJA behaviors of children with autism (Kasari et al., 1990). It was not the case, though, that children with ASD displayed significantly lower positive affect in requesting or turn–taking interactions. Hence, it was unlikely that the diminished positive affect in joint attention reflected a general aversion to social interactions. More recently, it has come to light that the onset of the systematic conveyance of positive affect as part of IJA bids begins to develop early in life, at about 8 to 10 months of age (Venezia, Messinger, Thorp, & Mundy, 2004) and that this type of anticipatory smiling in joint attention is associated with social outcomes in typical development (Parlade, Messinger, Delgado, Kaiser, Van Hecke, & Mundy, 2009). Thus, joint attention impairments reflect what are likely to be early arising deficits in the tendency of children with ASD to socially share positive affect. This in turn may involve a disturbance in their early appreciation of the positive social *value* of shared attention. That is to say, motivation factors or sensitivity to reward value of social gaze may play a role in joint attention disturbance in ASD (Dawson, Bernier, & Ring, 2012; Mundy, 1995).

Joint Attention and the Social-Cognitive Model of ASD

In a similar timeframe, other translational infant research groups in London began to translate Wimmer & Perner's basic false belief developmental paradigms to the study of ASD. This led to another sequence of seminal observations regarding the defining features of social impairments in ASD. Children with ASD appeared to have more difficulty with the development of social cognition than other aspects of cognitive development (e.g., Baron-Cohen, Leslie, & Frith, 1985; Frith, 1989; Leslie & Happé, 1989).

Thus, the parallel observations of deficits in joint attention development and theory of mind development in ASD during the mid-1980s provided the first empirical, albeit indirect, link between these two domains of development. Subsequently, the social cognitive view of ASD and typical social development became so compelling in the literature that joint attention disturbance began to be interpreted as a manifestation of social cognitive impairment in ASD (Baron-Cohen, 1989; Leslie & Happé, 1989). In developmental psychopathology, these ideas converged to form the social cognitive model of joint attention disturbance in ASD, which held that the social cognitive understanding that people intentionally share information, was a necessary precursor of joint attention (Tomasello, Carpenter, Call, Behne, & Moll, 2005), and that impairments in a social cognitive module explained the cause of joint attention impairment in ASD (Baron-Cohen, 1989).

The Disassociation of IJA and RJA in ASD

However, a potential problem for the social cognitive model is that both RJA and IJA development were assumed to

be equally dependent on social cognition. But IJA and RJA appeared to be dissociated in development. Thus one factor, such as social cognition, might not be adequate to explain all facets of joint attention development or its impairment in ASD. Both RJA and IJA are useful in the early identification and diagnosis of ASD (e.g., Lord et al., 2000; Stone, Coonrod, & Ousley, 1997). However, RJA impairments are less evident for children with more advanced levels of cognitive development (Mundy et al., 1994; Figure 4.10). Indeed, across studies of different age groups of children, there is at best inconsistent evidence of a robust syndrome specific impairment in the ability to process the direction of gaze or respond to joint attention in people with ASD (Nation & Penny, 2008). On the other hand, IJA deficits are observed in children with ASD from preschool through adolescence, *and* IJA is a better discriminator of children with ASD relative to children with other developmental disorders (e.g., Charman, 2004; Dawson et al., 2004; Hobson & Hobson, 2007; Mundy et al., 1986; Sigman & Ruskin, 1999). The correlates of IJA and RJA also diverge as much as they converge in studies of ASD. Both IJA and RJA are related to executive inhibition and language development in ASD (Bono, Daley, & Sigman, 2004; Dawson et al., 2002, 2004; Griffith et al., 1999; Sigman & McGovern, 2005). However, to our knowledge, only IJA is significantly associated with individual differences in social and affective symptom presentation (Charman, 2004; Kasari et al., 1990; Kasari et al., 2007; Lord et al., 2003; Mundy et al., 1994; Naber et al., 2008; Sigman & Ruskin, 1999).

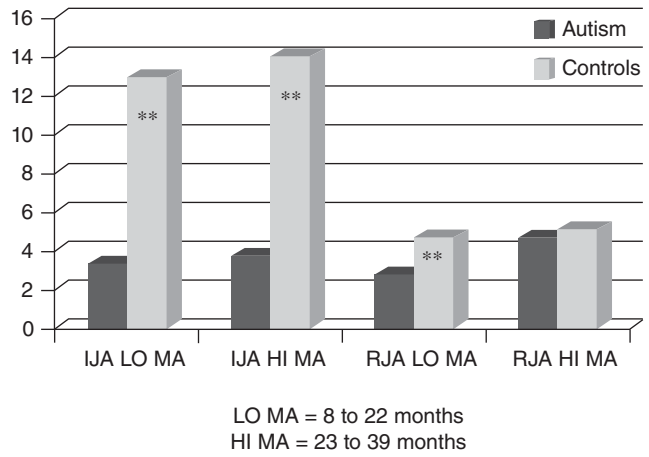


Figure 4.10 Illustration of the moderating effect of mental age on diagnostic group differences on RJA versus IJA. *Source:* Reported in P. Mundy, M. Sigman, & C. Kasari, Joint attention, developmental level, and symptom presentation in children with autism, *Development and Psychopathology, 6,* 389–401, 1994.

This literature emphasizes that joint attention deficits are neither absolute nor uniform in ASD, and the impairments of IJA and RJA likely constitute different developmental processes that are vital to symptom presentation in the syndrome. Moreover, of the two, deficits in initiating joint attention behavior appears be the more pathognomonic feature of ASD (Mundy, 1995). Observations from intervention research also emphasize that ASD is a disturbance of the spontaneous generation of social behaviors, as much as or more than a disturbance of perception and response to the social behaviors of others (Koegel et al., 2003). A similar interpretation is suggested by recent research with infant siblings of children with ASD (Zwaigenbaum et al., 2005). Indeed, the centrality of initiating deficits, especially IJA, was highlighted in the *DSM-IV*, where "a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people, (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)" was described as one of the primary social symptoms of ASD (APA, 1994, p. 75). Unfortunately, the significance of the impairment of the spontaneous generation of behavior, and specifically initiating joint attention, is still not fully appreciated in the field. Consequently, the latter is not as clearly emphasized in *DSM-5* (APA, 2013) as it was in *DSM-IV* (APA, 1994). Nevertheless, the gold standard research-based diagnostic observation instrument, the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2: Lord et al., 2012), continues to recognize the primacy of IJA symptoms. Measures of both IJA and RJA are used in Module 1 diagnostic algorithms for the youngest children. However, Module 2, for older or more linguistically advanced children, only includes IJA measures in its diagnostic criteria (Lord et al., 2012).

Evidence of a developmental dissociation between IJA and RJA is also apparent in studies of typical infant development. Frequency measures of IJA and RJA are characterized by different growth patterns, and these domains display weak to non-significant correlations in infant development (e.g., Meltzoff & Brooks, 2008; Mundy et al., 2007; Sheinkopf et al., 2004; Slaughter & McDonald, 2003). They also have different patterns of correlations with childhood IQ (Ulvund & Smith, 1996), frontal brain activity (Caplan et al., 1993; Mundy et al., 2000), reward-based behavioral goal-inhibition and self-monitoring behaviors (Nichols et al., 2005), attention related self-regulation (Morales et al., 2005), and attachment (Claussen, Mundy, Malik, & Willoughby, 2002). These observations imply that the nature of the differences, as well as commonalities,

between IJA and RJA may be a key to conceptualizations of the joint attention impairments of ASD.

Specific Effects on Initiating Joint Attention in ASD

It is essential to be precise about the nature of the behavioral expression of IJA impairments in ASD, which are often equated with problems with pointing and showing gestures. However, diminished alternating gaze behavior (Figure 4.1) is a more powerful measure of IJA impairment in ASD. This type of measure was superior to pointing and showing, and correctly identified 94% of 54 preschool children with ASD, mental retardation, and typical development (Mundy et al., 1986). Others have observed that IJA measured with the Early Social-Communication Scales (ESCS; Seibert, Hogan, & Mundy, 1982) had a sensitivity of 83–97% and a specificity of 63–67% in discriminating 3- to 4-year-olds with ASD from controls (Dawson et al., 2004). Recent research indicates that most of the variance in ESCS-IJA scores is carried by alternating gaze behavior (Mundy et al., 2007). The IJA alternating gaze of 2-year-olds also predicts 4-year-old symptom outcomes in children with ASD (Charman, 2004) as well as social cognition in typically developing 4-year-old children (Charman et al., 2000).

These developmental and measurement details are important for models of joint attention disturbance in ASD. Often joint attention problems are viewed as growing out of developmental antecedent or successor processes that are considered to be more fundamental. A nonexhaustive list here includes affective processes, reward-sensitivity, executive attention control, social orienting, identification, imitation and mirror neurons, intersubjectivity, and most prominently social cognition (e.g., Baron-Cohen, 1989; Charman, 2004; Dawson et al., 2004; Mundy et al., 1986; Williams, 2008). This reductionism has lead to a paradox where joint attention deficits are viewed as pivotal to ASD but also as an outgrowth of more basic processes. Charman (2004) recognized this paradox in noting that we often think of joint attention not as "a starting point [for ASD], but merely a staging post in early social communicative development, and hence a 'postcursor' of earlier psychological and developmental processes . . . [which may] underlie the impaired development of joint attention skills in autism" (p. 321).

There are at least three problems with this perspective. First, as previously noted, stable individual differences in IJA alternating gaze are well established by 8 to 9 months in typical development (Mundy et al., 2007; Venezia et al., 2004), and the onset of cortical control of alternating gaze likely begins between 4 to 6 months of age (Mundy, 2003; Striano & Reid, 2006). Joint attention precursors would need to be present prior to this time. Second, there is little evidence that the association of joint attention with the etiology or outcomes of ASD is mediated by more basic antecedent or successor processes. Dawson et al. (2004) observed that neither social-orienting measures nor empathy measures could account for relations between IJA and language development in a large sample of children with ASD. Joint attention disturbance in ASD also cannot be explained in terms of affect regulation or social relatedness measured with attachment measures (Capps, Sigman, & Mundy, 1994; Naber et al., 2008). Moreover, joint attention accounts for significant portions of variance in the language, symbolic play, and symptom development of children with ASD above and beyond variance associated with executive functions, imitation, knowledge about others' intentions, or global measures of mental development (e.g., Charman, 2004; Kasari et al., 2007; Naber et al., 2008; Roeyers, Van Oost, & Bothutne, 1998; Rutherford, Young, Hepburn, & Rogers, 2007; Sigman & Ruskin, 1999; Smith, Mirenda, & Zaidman-Zait, 2007; Thurm, Lord, Lee, & Newschaffer, 2007; Toth, Munson, Meltzoff, & Dawson, 2006).

A third issue is that precursor and successor process hypotheses rarely account for the dissociation of IJA and RJA (Mundy et al., 2007). Social-cognitive hypotheses suggest that RJA and IJA should be highly related because they are precursors of a common mentalizing ability involved in perceiving the intentions of others (e.g., Baron-Cohen, 1995; Tomasello, 1995). Executive attention or social-orienting hypotheses don't explicitly account for why IJA deficits are more pervasive than RJA deficits even though both ostensibly involve comparable attention inhibition and attention reorienting processes (e.g., Dawson et al., 1998; Mundy & Burnette, 2005). Imitation and mirror neuron theory emphasizes the role of deficits in processing and responding to the behavior of other people in the development of ASD (e.g., Williams, 2008). Hypothetically, though, this should be more related to responsive joint attention than the spontaneous initiation of joint attention bids. Why, then, do IJA deficits appear to be the more robust form of joint attention disturbance in ASD than RJA deficits? An answer may be perceived from a constructivist vantage point on joint attention and human social learning (e.g., Bruner, 1975, 1995).

In light of the assumption that joint attention is basic to early learning, reconsider the observation that IJA and RJA dissociate in development. Theory and research suggest that this occurs because these forms of joint

attention involve functions of two distinct neural networks that support attention development (Mundy & Newell, 2007). In conjunction with this idea, note that parallel and distributed cognitive theory suggests that learning occurs best in the context of the simultaneous activation of multiple neural networks during encoding (e.g., Munakata & McClelland, 2003; Otten, Henson, & Rugg, 2001). Taken together, these ideas raise two hypotheses. First, joint attention may involve the early development of a form of social information processing across multiple distributed neural networks. Second, ASD may be characterized by a developmental impairment of distributed neural connectivity, and an early disturbance of the cortically distributed joint attention network is a characteristic of the developmental etiology of many, if not all, children with ASD. The next, and final, section of this chapter will explore this second hypothesis, and its implications, in more detail.

APPLYING THE JOINT ATTENTION PDPM TO ASD

Neural Connectivity and Activity-Dependent Genes in ASD

Assumptions of the PDPM bridge theory on the development of joint attention with phenomena are observed in other disciplines of research with ASD. Several of these will be briefly considered in this final section of the chapter. The first of these involves links with theory and research on neural connectivity impairments in ASD.

Over the last 10 years, several research groups have suggested that problems in functional connectivity between brain regions contribute to ASD (e.g., Courchesne & Pierce 2005; Geschwind & Levitt, 2007; Horwitz, Rumsey, Grady, & Rapoport, 1988; Just, Cherkassky, Keller, & Minshew, 2004; Lewis & Elman, 2008; Wickelgren, 2005). However, rather than specific to ASD, impaired connectivity may be central to many forms of intellectual disability and developmental disorders (Dierssen & Ramakers, 2006). So how do neurodevelopmental connectivity impairments lead to the specific social symptom impairments of ASD, and how are these different from the connectivity impairments that characterize other developmental disorders?

One possibility is that intellectual disability may be associated with connectivity impairments within proximal brain networks, but that ASD may be characterized by more distal connectivity problems (Courchesne & Pierce, 2005; Lewis & Elman, 2008). Indeed, several studies suggest that distal connectivity problems between frontal and temporal-parietal networks may be especially prominent in ASD (Cherkassky, Kana, Keller, & Just, 2006; Courchesne & Pierce, 2005; Murias,Webb, Greenson, & Dawson, 2007; Wicker et al., 2008). The PDPM offers a moderately explicit developmental account of how the impairment of distal frontal-parietal pathways may have an early and robust effect specific to a disturbance of joint attention and related social symptoms of ASD, such as a lack of spontaneously sharing experiences with other people. The PDPM's focus on the fundamental relations between the joint processing of attention information, learning, and symbolic development also provide a means for understanding why variations in the strength of the disturbance of anterior-posterior connectivity could contribute to phenotypic variability in ASD, such as the co-occurrence of intellectual disability or specific language impairments.

The connectivity assumptions of the PDPM also lead to the prediction that differences in the development of joint attention in typical and atypical children should be associated with measures of synchrony or coherence in cortical activity. There is some support for this, but currently available data are no more than suggestive in this regard (Mundy et al., 2000, 2003). Nevertheless, the PDPM offers a conceptual framework that emphasizes the benefits of a multidisciplinary approach to neurodevelopment, attention, and connectionist network models of development and ASD. This emphasis is in line with the recent call for the multidisciplinary examination of EEG or imaging connectivity/coherence in developmental and intervention studies of ASD (Cicchetti & Toth, 2009; Dawson, 2008).

It also may be that intellectual disability is associated with impairments of prenatal neural connectivity that are less activity dependent, but that ASD involves a greater degree of postnatal connectivity impairments that are more activity dependent (Morrow, Yoo, Flavell, Kim, & Lin, 2008). Morrow et al. recently observed several genome deletions in families of children with ASD. The expression of three genes associated with the two largest deletions (c3orf58, NHE9, and PCDH10) is regulated by neuronal activity. From this observation, Morrow et al. (2008) reasoned that defects in activity-dependent gene expression may be a cause of cognitive deficits in ASD. They noted that these genes likely have a defined temporal course of greater or lesser vulnerability to atypical expression, depending on the timing and quality of the young child's postnatal activity and experience dependent processes.

The PDPM proposes that problems with initiating joint attention activity may be especially key to understanding activity dependent alterations of gene expression associated with ASD. Some evidence consistent with this proposition stems from the observation that the behavior of children with ASD may affect and modify the attempts

of caregivers to scaffold the development of joint attention in their children (Adamson, McArthur, Markov, Dunbar, & Bakeman, 2001). If the PDPM is correct in this regard, it will be important to build a better understanding of genetic influences on the typical range of expression of individual differences in IJA in infant development. Little if any information currently exists on this topic. Fortunately, the recent observation of a surprising degree of longitudinal stability of individual differences, in a sample of 100 typical infants (Mundy et al., 2007), suggests that behavioral or metabolic genetic methods may be brought to bear in large-scale studies of the typical development of infant joint attention.

Visual Attention Control and Joint Attention in ASD

Complementary to genetic factors, the work of several research groups indicates that the basic mechanism of visual control may play a role in ASD (Brenner, Turner, & Muller, 2007; Johnson et al., 2005; Landry & Bryson, 2004). Brenner et al. (2007) noted that one of the essential issues for this line of research is to understand precisely, "how an ocular-motor system that is over-specialized for certain tasks and under-specialized for others early in life might affect later development in [social] domains such as joint attention" (p. 1302). The PDPM offers a guide in this regard. First, it encourages the research community to recognize the possibility that joint attention may not be a later development but one that begins as part of the development of volitional visual attention control by the fourth month of life. In addition, the PDPM provides a means for understanding how significantly altered early visual preferences could have a cascading effect on the development of intentional joint attention and ASD (Mundy, 1995). In this regard, consider two recent studies.

McCleery et al. (2007) observed that magnocellular visual processing may be atypically enhanced in a sample of 6-month-old infant siblings of children with autism. Similarly, Karmel et al. (2008) observed visual attention patterns that are consistent with a magnocellular bias in 6-month-olds in neonatal intensive care who later received the diagnosis of autism at 3 years of age. The magnocellular visual system contributes to orienting based on movement and contrast-sensitivity related to small achromatic differences in brightness. This system dominates early visual orienting. However, by 2 to 4 months of age, visual orienting is increasingly influenced by the parvocellular system, which contributes to orienting based on high-resolution information about shape or low-resolution information about color and shades of gray. Karmel et al. (2008) and McCleary et al. (2007) raised the possibility that a delay in the developmental shift from the magnocellular to parvocellular visual systems could alter what children with ASD choose to attend to early in life.

Hypothetically, the maintenance of a magnocellular bias may lead to a relatively long standing visual preference for stimuli or objects characterized by movement or achromatic contrasts, such as surface edges, power lines, spinning objects, the outlines of faces, or mouth movement. Reciprocally, the decreased influence of the parvocellular system could lead to developmental delays in the emergence of a visual attention bias to targets that are socially informative but involve differentiation based on high resolution of shape and color information, such as distal processing of eyes and facial expressions. Thus, the alteration of visual preferences during early critical periods of development could degrade the establishment of the dynamic system of internal information processing about active looking, relative to contingent social feedback, and information about the attention of other people (Mundy, 1995; Mundy & Burnette, 2005). Moreover, if magnocellular guidance bias and connectivity impairments are orthogonal processes, combinations of varying levels of their effects could present as phenotypic differences in joint attention processing and social symptom expression in ASD.

Joint Attention, Learning, and Interventions for ASD

The assumptions of the PDPM may also shed light on how joint attention serves as a pivotal skill in intervention, and as a foundation for the development of social cognition, symbolic thought, knowledge of intentionality, and social learning. First, the PDPM may help to explain why joint attention is a pivotal skill in early intervention for children with autism (Bruinsma, Koegel, & Koegel, 2004; Charman, 2004; Mundy & Crowson, 1997). Improvements in pivotal skills, by definition, lead to positive changes in a broad array of other problematic behaviors. According to the PDPM, joint attention is a pivotal skill in autism because its improvement has multiple effects on social learning. Recall that joint attention facilitates the self-organization of information processing to optimize incidental, as well as structured, social learning opportunities (Baldwin, 1995). Hence, impairment in joint attention may be viewed as part of a broader social-constructivist learning disturbance in autism. By the same token, effective intervention likely improves social constructivist learning in autism.

Small and large-scale trials have shown that joint attention can be improved with intervention for ASD (Table 4.1), and joint attention improvement has collateral

TABLE 4.1 Behavioral Intervention Studies With Effects on Joint Attention in Children With ASD[1]

Study	Intervention	Design	Participants in experimental treatment group (number/age)	JA outcomes
Small studies (fewer than 15 participants in experimental treatment group)				
Aldred, Green, and Adams (2004)	Developmental communication intervention (Aldred, Phillips, Pollard, & Adams, 2001)	RCT (vs. routine community care control)	14/2–5 yrs.	No change in CJA
Baker (2000)	Thematic ritualistic play intervention	MBL by participants	3/5–6 yrs.	Increase in CJA
Cheng and Huang (2012)	Joint Attention Skills Learning (JASL) virtual reality system/tool	MBL by participants	3/9–12 yrs.	Increase in IJA
Ezell et al. (2012)	Imitation	RCT (vs. Contingently Responsive Play control)	10/4–6 yrs.	Increase in IJA and RJA
Field et al. (1997)	Touch therapy	RCT (vs. non-therapeutic touch control)	11/mean 4 yrs., 6 mo.	Increase in RJA and IJA
Hwang and Hughes (2000)	Social interactive training: following child, imitation, natural reinforcement	MBL by participants	3/2–3 yrs.	Increase in IJA
Ingersoll and Schreibman (2006)	Reciprocal imitation training	MBL by participants	5/2–3 yrs.	Increase in RJA; Mixed results for IJA
Ingersoll (2012)	Reciprocal imitation training	RCT (vs. community treatment control)	14/2–4 yrs.	Increase in IJA
Isaksen and Holth (2009)	Reinforcement, prompting, modeling	MBL by participants	4/3–5 yrs.	Increase in IJA and RJA
Jones, Carr, and Feeley (2006)	Pivotal response training; discrete trial	MBL by behaviors and participants	5/2–3 yrs.	Increase in IJA and RJA
Jones and Feeley (2007)	Pivotal response training; discrete trial; parent training	MBL by behaviors and participants	3/3–4 yrs.	Increase in IJA and RJA
Jones (2009)	Pivotal response training: modeling, prompting	MBL by behavior	2/3–5 yrs.	Increase in IJA
Klein, MacDonald, Vaillancourt, Ahearn, and Dube (2009)	Reinforcement	MBL by participants	3/4–6 yrs.	Increase in RJA
Krstovska-Guerrero and Jones (2013)	Direct instruction of smiling and eye contact, prompting, reinforcement	MBL by participants and behaviors	3/2–4 yrs.	Increase in IJA and RJA
Lawton and Kasari (2012)	JASP/ER: Joint Attention symbolic play engagement and regulation intervention; teacher implemented	RCT (waitlist control)	9/3–5 yrs.	Increase in IJA
MacDuff et al. (2007)	Auditory scripts, reinforcement	MBL by participants	3/3–5 yrs.	Increase in IJA
Martins and Harris (2006)	Reinforcement	MBL by participants	3/3–4 yrs.	Increase in RJA; No change in IJA
Naoi et al. (2008)	JA reinforcement, modeling, preferred objects	MBL by participants	3/5–8 yrs.	Increase in IJA
Pierce and Schreibman (1995)	Pivotal response training; peer implemented	MBL by participants	2/10 yrs.	Increase in CJA
Rocha, Schreibman, and Stahmer (2007)	Parent training: discrete trial, pivotal response training	MBL by participants	3/2–4 yrs.	Mixed results for IJA and RJA
Rogers et al. (2006)	Early Start Denver Model (ESDM)	RCT (vs. prompts for restructuring oral muscular phonetic targets (PROMPT) control); MBL for participants and behaviors	5/2–5 yrs.	Mixed results for IJA and RJA for both interventions
Salt et al. (2002)	Scottish Center for Autism treatment program: Social developmental naturalistic intervention	Treatment (vs. waitlist control, not randomized)	14/3–4 yrs.	Increase in IJA and RJA (collapsed)
Schertz and Odom (2007)	Joint attention mediated learning (JAML) intervention (Schertz, 2005)	MBL by behaviors	3/1–2 yrs.	Mixed results for IJA and RJA
Schertz, Odom, Baggett, and Sideris (2013)	Joint attention mediated learning (JAML) intervention	RCT (vs. community treatment control group)	11/1–2 yrs.	Increase in RJA; No change in IJA

(*continued*)

TABLE 4.1 (*Continued*)

Study	Intervention	Design	Participants in experimental treatment group (number/age)	JA outcomes
Stickles Goods, Ishijima, Chang, and Kasari (2013)	JASP/ER: joint attention symbolic play engagement and regulation intervention	RCT (vs. community intensive Applied Behavior Analysis treatment control)	7/3–5 yrs.	No change in IJA
Taylor and Hoch (2008)	Behavioral: prompting, reinforcement	MBL by participants	3/3–8 yrs.	Increase in IJA and RJA
Tsao and Odom (2006)	Sibling mediated: stay, play, talk	MBL by participants	4/3–6 yrs.	Increase in CJA
Vismara and Lyons (2007)	Parent training, Pivotal response training; follow child's lead	Reversal; MBL by participants and behaviors	3/2–3 yrs.	Increase in IJA
Vismara and Rogers (2008)	Early Start Denver Model (ESDM: Rogers & Dawson, 2007)	Case study	1/1 yr.	Increase in IJA
Whalen and Schreibman (2003)	Pivotal response training; discrete trial	MBL by participants	5/4 yrs.	Increase in RJA; Mixed results for IJA
Zercher et al. (2001)	Peer-supported play, modeling	MBL by participants	2/6 yrs.	Increase in RJA; Mixed results for IJA
Large studies (15 or more participants in experimental treatment group)				
Green et al. (2010)	Preschool Autism Communication Trial (PACT)	RCT (vs. community treatment as usual)	77/2–4 yrs.	Increase in CJA
Gulsrud, Kasari, Freeman, and Paparella (2007)	Targeted joint attention intervention (based on Kasari et al., 2006)	RCT (vs. Symbolic Play Intervention control)	17/2–4 yrs.	Increase in CJA
Kaale, Smith, and Sponheim (2012)	Targeted joint attention intervention, based on Kasari et al. (2006)	RCT (vs. community preschool program control)	34/2–5 yrs.	Increase in IJA
Kasari, Freeman, and Paparella (2006)	Targeted joint attention intervention	RCT (vs. symbolic play intervention vs. control in existing early intervention program)	20/3–4 yrs.	Increase in IJA, CJA, and RJA
Kasari, Paparella, Freeman, and Jahromi (2008)	JASP/ER: joint attention symbolic play engagement and regulation intervention (6- and 12-month follow-up to sample in Kasari et al., 2006)	RCT (vs. symbolic play intervention vs. control in existing early intervention program)	20/3–4 yrs.	Increase in IJA and CJA
Kasari, Gulsrud, Wong, Kwon, and Locke (2010)	Focused joint attention intervention; parent training (based on Kasari et al., 2006)	RCT (vs. waitlist control)	19/2–3 yrs.	Increase in RJA; No change in IJA
Landa, Holman, O'Neill, and Stuart (2011)	Interpersonal synchrony intervention	RCT (vs. noninterpersonal synchrony intervention)	24/1–2 yrs.	No change in IJA in either intervention
Wong, Kasari, Freeman, and Paparella (2007)	Behavioral (prompting, social/natural reinforcement, imitation) joint attention intervention	RCT (vs. symbolic play intervention in existing early intervention program)	20/3–4 yrs.	Increase in IJA
Yoder and Stone (2006)	Responsive education and prelinguistic milieu teaching (RPMT)	RCT (vs. PECS: picture exchange communication system, Bondy & Frost, 1994, control)	16/1–3 yrs.	Increase in IJA in both treatments; children with >10 IJA acts at pretest had greater gains from RPMT; children showing < 2 IJA acts at pretest had greater gains from PECS

[1] IJA = initiating joint attention. RJA = responding to joint attention. CJA = coordinated joint attention. RCT = randomized controlled trial. MBL = multiple baseline design. Studies were included in this table if (1) a behavioral treatment, with or without a specific focus on joint attention, was employed with children with autism, autism spectrum disorder, or pervasive developmental disorder–not otherwise specified, and (2) either RJA, IJA, or CJA was assessed before and after the employed treatment. Typical measurement for RJA and IJA included various paradigms, such as gaze-following tasks, individual IJA, or RJA scores from the Autism Diagnostic Observation Schedule (Lord, Rutter, Dilavore, & Risi, 1999), or the Early Social Communication Scales (ESCS: Mundy, Hogan, & Doehring, 1996), among others. CJA was typically measured as a proportion of time children were engaged in focused, cooperative, free play with an adult or peer, wherein gaze alternating and eye contact occurred.

benefits on language as well as cognitive and social development (Jones, Carr, & Feely, 2006; Kasari et al., 2007; Rudd, Cain, & Saxon, 2008; Whalen, Schreibman, & Ingersoll, 2006). At this point, the bulk of large-scale trial evidence (see Table 4.1) for the malleability of joint attention in young children with ASD originates from the JASP/ER (Kasari et al., 2006) intervention at UCLA which focuses on joint attention as a primary intervention target and outcome. One other large-scale intervention (Green et al., 2010) focusing on communication, more generally, reported increases in bouts of coordinated joint attention between children with ASD and caregivers. Thus, it will be important for future ASD intervention studies to also report specific pre-test and post-test measurements of joint attention. This type of data will enable researchers to determine whether joint attention improvements must be specifically targeted by intervention, or whether joint attention can improve as a function of general positive treatment response to nonspecific interventions. Further, understanding the effects of intervention on joint attention will likely elucidate the mechanisms of healthy social development (Cicchetti & Toth, 2009). Joint attention also appears to mediate responsiveness to early intervention among children with autism (Bono et al., 2004; Yoder & Stone, 2006).

Second, the PDPM proposes that joint attention serves as a foundation for social-cognitive development. Social-cognitive development is defined in terms of advances in the processing of information about self and other, rather than singularly in terms of changes in knowledge about intentionality. Following connectionist cognitive theory (McClelland & Rogers, 2003; Otten, Henson, & Rugg, 2001), the PDPM assumes that information encoded during learning is stored as a distributed neural network activation pattern that involves parallel activation of networks of related semantic information. Additionally, whenever information is acquired during social learning and joint attention, it is also encoded in parallel with the activation of a frontal-temporal-parietal neural network that maps relations between representations of information about self-directed attention and information about the attention of other people. Thus, every time we process information in social learning, we encode it as an activation pattern in a distributed semantic network *in conjunction with* an activation pattern of the anterior-posterior cortical joint attention network (Figure 4.4, Figure 4.5). Recall that deeper information processing and learning occurs best in the context of the simultaneous activation of multiple neural networks during encoding (Otten et al., 2001). If so, joint attention may lead to deeper processing because it adds activation of the distributed social attention network (a form of episodic encoding) to the network activation associated more directly with semantic information. This conjecture provides one interpretation of the observation that joint attention facilitates depth of processing in 9-month-olds (Striano, Chen, Cleveland, & Bradshaw, 2006; Striano, Reid, & Hoel, 2006). It also suggests that part of the learning disability of ASD occurs because children with this disorder do not reap the full benefits of encoding semantic information in conjunction with episodic memory encoded within the integrated processing of self- and other-attention (Mundy et al., 2010).

Some evidence has recently been provided by a sequence of studies of the effects of joint attention on the recognition memory of adults and older children. A recent study has used a virtual reality paradigm to study the effects of picture recognition in college students (Kim & Mundy, 2012). In this study, participants studied pictures of faces, houses, or abstract designs under one of two conditions: (1) the avatar followed the gaze of participants to target pictures on study trials (IJA condition); or (2) participants followed the gaze of an avatar to target pictures on study trials (RJA condition; Figure 4.11). The results of the study indicated that adults correctly recognized significantly more pictures in the IJA than the RJA condition. There are several possible reasons for IJA-related information processing superiority. One is that self-initiated target choice is coupled with better or easier processing than directed target choice. Another possibility is that having another person or avatar follow one's gaze to an object, and the experience of directing or controlling another person's gaze, changes the perception and processing of the common focus of attention (Bayliss, Paul, Cannon, & Tipper, 2006; Mundy & Jarrold, 2010). More interesting, for the topic at hand, the paradigm used by Kim and Mundy (2012) was recently presented to 30 higher functioning children with ASD and 50 age-, gender-, and IQ-matched typically developing children (Kim et al., in preparation). The results indicated that the typically developing children displayed an advantage of picture recognition memory in the IJA condition versus the RJA condition, which was comparable to the pattern of data Kim & Mundy (2012) reported for adults. Moreover, the typically developing sample displayed significantly better performance in the IJA condition than the RJA condition, but the ASD sample did not display any differences in recognition memory across the IJA and RJA conditions. These data are consistent with the notion that, in childhood, joint attention does not affect information processing in children with ASD in a manner that is comparable to effects observed for children without ASD.

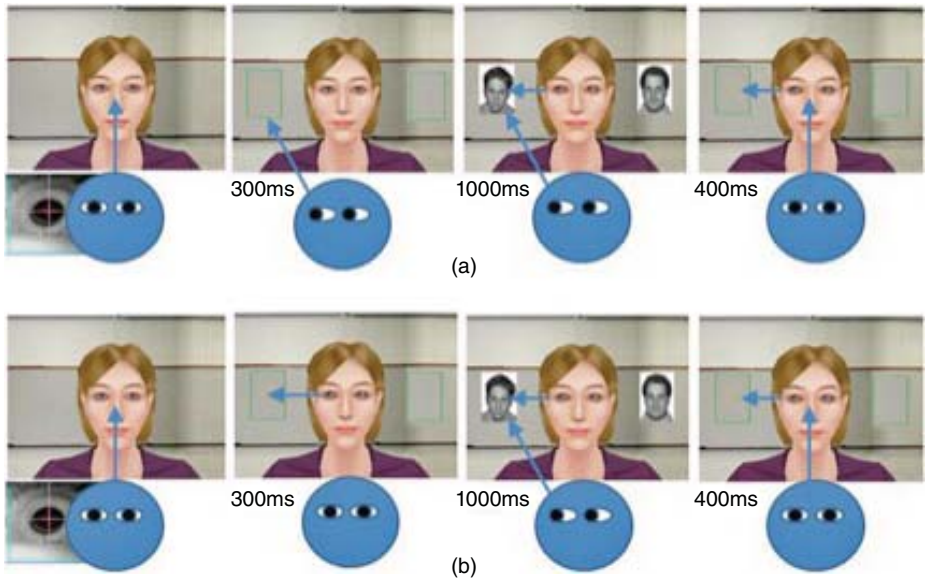


Figure 4.11 Illustration of the IJA and RJA conditions in the Kim & Mundy (2012) joint attention and memory paradigm. In the IJA condition (panel A), the participant first views the avatar, then chooses to shift attention to a stimulus window to the left or right of the avatar. Eye-tracking data then flows to a WorldViz© software program to trigger gaze following in the Avatar and onset of the study picture. The final illustration in panel A indicates that, after a study trial ended, the participant returned to midline, but the Avatar remained fixated on the target area to insure that the participant recognized that the avatar had followed his or her gaze. In the RJA condition, the participant fixated the Avatar and followed the direction of gaze of the avatar to choose a picture to study. Eye tracking control of stimulus onset ensured the picture did not appear until the participant followed the Avatar's gaze. This equated the study time that was available on each trial across IJA and RJA conditions. The Avatar again returned to midline gaze after the participant returned to midline. See footnote 1. *Source:* Reprinted with permission from Kim and Mundy (2012).

A third argument of the PDPM is that overt joint attention becomes increasingly internalized as a social-executive function that supports the social coordination of covert mental attention to cognitive representations. The spontaneous coordination of mental attention and cognitive representations is an essential element of symbolic thought (Tomasello et al., 2005). The PDPM assumes that months of practice of the social coordination of overt attention (i.e., joint attention) in the first years of life is required before this function can be internalized and transformed to an executive facility for socially coordinated covert mental attention and symbolic thought. Thus, symbolic thought processes incorporate, but do not replace, activation of the self-other joint attention system. Joint attention, on the other hand, does not necessarily involve symbolic processes (Mundy et al., 1987). These assumptions of the PDPM are consistent with two recent observations. Joint attention is a unique predictor of pretend play development in children with ASD relative to measures of imitation or executive functions (Rutherford et al., 2007). Moreover, successful symbolic play intervention, which according to the PDPM must involve effects on joint attention, *is* associated with parallel collateral improvements in joint attention in autism. However, intervention with joint attention has less immediate impact on symbolic play behavior (Kasari et al., 2006).

Fourth, the joint processing of attention information also plays a fundamental role in social cognition, defined in terms of the development of knowledge about intentions in self and other (Mundy & Newell, 2007). The assumption here is that when infants or primates practice monitoring others' attention (RJA), statistical learning ultimately leads to the associative rule: *where others' eyes go, their behavior follows* (Jellema, Baker, Wicker, & Perrett, 2000). Similarly, anterior monitoring, or self-awareness of control of visual attention, likely leads to awareness of the self-referenced associative rule: *where my eyes go, my intended behavior follows* (Mundy & Newell, 2007). An integration of the development of these concepts leads to the logical cognitive output: *where others eyes go → their intended behavior follows*, which is a building block of social-cognitive development (Mundy & Newell, 2007). Social cognition of this kind is thought to enable new and more efficient levels of social or cultural learning, and is atypical in ASD.

Finally, the constructivist assumptions of the PDPM stress that motivation factors are part of a crucial fifth path

of association between joint attention and social learning. Initiating joint attention requires "choosing" between behavior goals, such as fixated looking at an event, or alternating looking to the event and another person. Choosing among behavior goals is thought to involve frontal and medial cortical processing of the relative reward associated with different goals (Frank & Claus, 2006; Holroyd & Coles, 2002). Therefore, IJA impairment in ASD may be expected to be related to deficits in biobehavioral processes associated with reward sensitivity and motivation (Dawson, 2008; Kasari et al., 1990; Mundy, 1995). Such a deficit, however, could take several forms.

Social stimuli could be aversive in some way for children with ASD. However, the aversion hypothesis is complicated by observations of behaviors indicative of relatively intact caregiver-attachment in many children with ASD and a willingness to engage in playful physical interactions with strangers (e.g., Mundy et al., 1986; Sigman & Ungerer, 1984). On the other hand, social stimuli may not be aversive. Rather, social stimuli may simply not be sufficiently positive to compel social-orienting and joint attention early in the life of children with ASD (Dawson et al., 1998, 2012; Mundy, 1995). Finally, social stimuli could have a positive valence for children with ASD, but be overshadowed by an atypically strong visual preference that make objects, rather than social elements of the world, more interesting (Karmel, Gardner, Swensen, Lennon, & London, 2008; McCleary, Allman, Carver, & Dobkins, 2007; Mundy & Crowson, 1997).

The construction of effective empirical approaches to address these alternatives is one of the outstanding challenges in the science of ASD (Dawson, 2008; Koegel et al., 2003). Research on joint attention, in relation to motivation and the perceived valence of objects in adults (Bayliss et al., 2006), offers one potential route for developmental and functional neurocognitive studies on this topic. For now, though, the literature on intervention in ASD may be the best source of information in this regard. Early intervention studies offer some of the most systematic investigations to date of how to structure social engagements with young children with ASD to modify and increase their motivation to initiate episodes of shared attention and shared experience with others (e.g., Kasari et al., 2006, 2007). The impact of these interventions on the social development of children, their relationships to other people and the world, and transactional effects on their brain development and pathways to resilience (Cicchetti & Toth, 2009), cannot be underestimated.

SUMMARY

Only in its most expansive or grandiose interpretation can the PDPM be viewed as an explanatory model of joint attention, or ASD. Nevertheless, the PDPM does serve a purpose. It presents a new perspective on joint attention that suggests its impairment in ASD is more than an epiphenomenon associated with other fundamental precursor or successor processes. Rather, an impairment in joint attention constitutes a cardinal disruption in the process of healthy social development (Cicchetti & Toth, 2009), that then goes on to further affect social-behavioral development and neural development. This alternative perspective can be summed up in terms of several general principles.

First, ASD is as much about impairments in self-generated activity as it is about problems in perceiving or responding to the behavior of others. Hence, we need to consider the neurodevelopmental processes and networks involved in initiating behavior and attention control, as well as those involved in perceiving and responding to the behaviors of others, to understand this disorder (Mundy, 2003). Second, joint attention and social cognition are forms of information processing that give rise to knowledge, but their development may not be wholly defined in terms of stages of knowledge acquisition. Third, joint attention is a form of parallel processing because it involves the conjoint perception and analysis of information about self-attention and the attention of other people. This conjoint analysis of information also involves distributed processing across an anterior cortical system for guidance and self-monitoring of internal information about goal-directed attention, and a posterior cortical system for processing external information about the attention-related behavior of other people.

The third principle of the PDPM encourages a multidisciplinary approach to better link constructivist, connectionist neuroscience with parallel and distributed processing impairments in future research on ASD. Exemplary multidisciplinary efforts of this kind have already been published (e.g. Cohen, 2007; Lewis & Elman, 2008). However, the PDPM suggests that such efforts may be better informed with the appreciation of the following hypotheses. A disturbance of a distributed cortical system specifically involved in self-other representational mapping may be at the heart of human social cognition (Decety & Sommerville, 2003), and joint attention may be at the heart of the development of this quintessential form of human cognition, as well as its impairments in ASD.

This leads to the fourth principle of the PDPM. Joint attention is a social executive process that supports all forms of cognition that involve coordinating attention and knowledge about self and others, such as symbolic thought. Thus, neural network activation associated with joint attention is an enduring substrate that plays a role in the unique characteristics of human cognition throughout the life span (Mundy & Newell, 2007). Indeed, it may be one example of the type of hot executive function that Zelazo, Qu, and Muller (2005) theorized are central to social cognition. Hot executive functions are those that entail motivation processes and affect regulation specific to the support of successful goal-directed behavior in social engagement. Following from this notion, the fifth and final principle of the PDPM is that individual differences in the operation of the social executive function of joint attention may be an expression of variance in motivation processes.

FUTURE DIRECTIONS

One of the strengths of the PDPM in application to ASD research is that of hypothesis generation. The model proposes that joint attention is a fundamental, early-developing skill that supports the development of language, social connectedness, social cognition and learning, and social-emotional regulation. This skill is supported by a distributed neural network that integrates information about self (anterior) and other (posterior), and progresses from a learning phase into a routine phase via experience–expectant processes. The first question that follows from this model involves neural plasticity and the development of joint attention. Specifically, studies are needed that assess the development of joint attention and the concurrent development of the PDPM neural network, in typically developing samples, and in ASD samples undergoing interventions. A disruption in joint attention development may have a cardinal role in the endurance of social challenges across the lifespan in ASD, even as other challenges remit. This endurance may be due to the disturbance in the cycle of healthy social development, wherein shared attention and connectedness with others serves as crucial experience that propels brain development, activity, and structure, which then further constrains social abilities and stimulation over time. In light of this idea, prevention trials (Cicchetti & Toth, 2009), which assess whether neurophysiological domains are affected by treatments, are urgently needed. It will also be important to assess multiple levels of effect, such as neurophysiology, genetics, social behavior, and relationships with others, as all of these feed into the stimulation available to a developing organism. Recent work (e.g., Bolte et al., 2006; Faja et al., 2012; Vaughan Van Hecke et al., 2013) established that neural plasticity in response to intervention is possible in ASD and that white matter integrity is linked to early onset and duration of intervention (Pardini et al., 2012). One study reported increases in parietal-temporal EEG activity, perhaps reflective of the posterior network of the PDPM, in toddlers with ASD undergoing early, intensive intervention (Dawson et al., 2012). Thus, it will be critical, for our understanding of the syndrome, that we establish whether the PDPM is responsive to intervention for ASD and whether there are critical periods that bind this possibility. Additionally, it will be the task of similar studies to determine whether epigenetic effects of amelioration of joint attention deficits occur in response to interventions for ASD. Lastly, studies are needed that describe and measure joint attention across the life span. Although joint attention is well characterized in infancy and early childhood, very little is known about the progression of this uniquely human capability across the latter half of the life span. Studies that assess joint attention and PDPM neural function in adulthood and aging will be informative in this regard. In sum, understanding the nature of these processes, such as the degree to which they are mediated by learning processes or endogenous neural mechanisms, is a vital goal for future multidisciplinary developmental research on social cognition and ASD.

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CHAPTER 5

Explicating the "Developmental" in Preschool Psychopathology

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Over the past few decades, considerable progress has been made in the field of preschool psychopathology. There is now broad consensus that impairing, stable psychological conditions can be identified in a reliable and valid manner in young children (Dougherty, Leppert, et al., 2015; Egger & Angold, 2006). These research endeavors, coupled with increasing understanding of etiological processes in the development of early-emerging psychopathology, are essential to inform prevention and early intervention efforts to minimize the extent to which emotional and behavioral problems and associated impairment accumulate over time and impact children's development. Although much has been done, the next frontier in developmental psychopathology research is developmental specification of syndromes in a manner that sensitively differentiates normative variation from early emergence of atypicality and links this process to mechanisms. Given behavioral and neural plasticity in early childhood, detecting and treating emergent psychopathology and associated vulnerabilities in a manner that differentiates them from transient variability will be more effective than treatment of frank disorder after it becomes entrenched.

This chapter will focus on common emotional and behavioral syndromes that arise during the preschool period, including attentional, disruptive (oppositional and conduct), anxiety, and mood (i.e., depression) problems. Current knowledge based on the *Diagnostic and Statistical Manual* (*DSM*) will be summarized briefly to examine the state-of-the-science within the context of prior work. In keeping with the developmental psychopathology approach (Cicchetti, 1984; Cicchetti & Toth, 2009; Sroufe, 1979; Sroufe & Rutter, 1984) and novel conceptualizations of the underpinnings of mental disorder such as the Research Domain Criteria (RDoC; Cuthbert & Insel, 2013; Franklin, Jamieson, Glenn, & Nock, 2015; Insel et al., 2010; Sanislow et al., 2010), the central focus of the chapter will be an examination of preschool psychopathology within a dimensional, developmental domain framework as we see this as the next crucial advance for developmental psychopathology research. We will first describe measurement advances in the dimensional operationalization of behavior in preschool-age children. Next, we delineate broad developmental domains and their expression in early childhood as an example of a developmental approach

for establishing the normal–abnormal spectrum, including essential developmental capacities, their normative variation, and clinically concerning deviation within each domain. To further explicate each domain, we highlight developmental processes relevant to an exemplar diagnostic category. We also delineate steps for translating dimensional, developmentally sensitive measurement from research to clinical application. We will conclude with suggestions for future directions for research that are geared toward advancing multilevel, developmentally oriented conceptualization of psychopathology.

PRESCHOOL PSYCHOPATHOLOGY: WHAT HAVE WE LEARNED FROM A TRADITIONAL CATEGORICAL DSM-BASED APPROACH?

Over the past decade, it has become increasingly clear that common pediatric emotional and behavioral disorders often onset in early childhood. Sizable proportions of preschool-age children meet criteria for a range of *DSM* disorders. Overall, approximately one in five preschool-age children meets criteria for at least one psychiatric disorder (Dougherty, Leppert, et al., 2015; & Angold, 2006). This rate is similar to rates identified in older children and adults, and lends additional support to the notion that mental health problems often emerge early and persist throughout the life span. More specifically, in community samples of preschool-age children utilizing interview-based methods to establish clinical significance, overall rates of *DSM-IV* disorders in community samples range from approximately 16 to 27% (Bufferd, Dougherty, Carlson, & Klein, 2011; Egger, Erkanli, Keeler, Potts, Walter, & Angold, 2006; Ezpeleta, de la Osa, & Domenech, 2014; Wichstrøm et al., 2012).

In this section, we will provide a brief review of the rates of common *DSM* disorders (ADHD, disruptive behavior [DB; i.e., oppositional and conduct], anxiety, and mood disorders). Although there is a large literature on symptom and syndrome scales that laid the foundation for the field (e.g., Achenbach, Edelbrock, & Howell, 1987; Moreland & Dumas, 2008), this section will focus primarily on recent large community-based studies that assessed *DSM-IV* diagnoses using structured diagnostic interviews (Bufferd et al., 2011; Egger, Erkanli, et al., 2006; Ezpeleta et al., 2014; Keenan et al., 2007; Lavigne, Lebailly, Hopkins, Gouze, & Binns, 2009; Wichstrøm et al., 2012). In addition, we will discuss comorbidity among diagnoses. Next, we will summarize the available reliability and validity data relevant to *DSM* diagnoses. Finally, we will review measurement advances in the diagnostic assessment of preschool psychopathology and conclude the section with a discussion of the limitations of the *DSM* approach for capturing psychopathology in young children within developmental context.

In community-based studies that assessed *DSM-IV* diagnoses using structured diagnostic interviews, the range of rates of ADHD is 1.9–11.4%, and of DBDs is 1.8–12.1% for oppositional defiant disorder (ODD) (Bufferd et al., 2011; Egger, Erkanli, et al., 2006; Ezpeleta et al., 2014; Lavigne et al., 2009; Wichstrøm et al., 2012) and 0.7–3.3% for conduct disorder (CD) (Egger, Erkanli, et al, 2006; Ezpeleta et al., 2014; Wichstrøm et al., 2012). As this section focuses on traditional *DSM* categorical diagnoses, we have reported on CD separately from ODD. However, the distinction between ODD and CD at preschool age is questionable. Few studies have examined CD in this age group due to the developmental impossibility and improbability of most CD symptoms for young children (Wakschlag, Leventhal, Thomas, & Pine, 2007). Of those studies that have examined CD as a separate disorder, virtually all children who meet criteria also meet criteria for ODD (Keenan et al., 2007). Psychometric analyses suggest a common disruptive behavior factor and separate ADHD factor best fit the data at this age (Sterba, Egger, & Angold, 2007; Strickland et al., 2011). Overall, rates of anxiety disorders range from 1.5–19.6% (Bufferd et al., 2011; Egger, Erkanli, et al., 2006; Ezpeleta et al., 2014; Wichstrøm et al., 2012), with rates of individual disorders as follows: separation anxiety disorder (0.3–5.4%), specific phobia (0.7–9.1%), generalized anxiety disorder (GAD; 0.1–3.9%), social phobia (0.5–4.4%), agoraphobia (3.5%) and selective mutism (0.6–1.5%). Compared with other diagnostic areas, rates of depression diagnoses in preschoolers have been less well-studied. In the few studies that have assessed depression, rates range from 0.3–3.4% (Bufferd et al., 2011; Egger, Erkanli, et al, 2006; Ezpeleta et al., 2014; Lavigne et al., 2009; Wichstrøm et al., 2012). Across disorders, fairly wide ranges of rates are found and due, in part, to different instruments used, different numbers of disorders assessed (e.g., different number of individual anxiety disorders assessed), different age ranges within the preschool period, and samples recruited from a variety of geographic regions (Bufferd et al., 2011; Wakschlag, Leventhal, et al., 2007).

Similar to older children, adolescents, and adults, comorbidity among diagnoses is common in preschool-age children (Egger & Angold, 2006; Lavigne et al., 2009): rates range from 5.1 to 9.2% of preschoolers meeting criteria for two or more diagnoses. Studies have identified associations

between depression and ODD, anxiety and depression, anxiety and DBDs, and DBDs and ADHD (Bufferd et al., 2011; Egger & Angold, 2006; Ezpeleta et al., 2014; Lavigne et al., 2009; von Klitzing et al., 2014; Wichstrøm et al., 2012). When examining patterns of comorbidity, ODD emerges as commonly co-occurring with disorders in each of the other main diagnostic categories; similar findings have been identified in older children (Angold, Costello, & Erkanli, 1999; Ford, Goodman, & Meltzer, 2003) and are consistent with research on the cross-cutting role of irritability in contributing to later psychopathology (Dougherty, Smith, et al., 2013; Dougherty, Smith et al., 2015; Dougherty et al., 2015; Stringaris, Cohen, Pine, & Leibenluft, 2009).

The Measurement of Preschool Psychopathology

This work in identifying *DSM* disorders in young children has rested on critical measurement advances that provided an early childhood framework for clinical assessment of preschool-age children. The area of preschool psychopathology was built initially on the use of checklist measures to assess both broad (e.g., Achenbach & Rescorla, 2000; McGuire & Richman, 1986) and specific (e.g., Campbell & Breaux, 1983) symptom domains in young children. These early checklist methods offered feasible approaches for assessing problem behavior patterns and determined clinical thresholds quantitatively. However, limitations of this approach include limited assessment of severity or pervasiveness, and reliance solely on respondents' knowledge to interpret the meaning of their children's behaviors and estimate the relative frequency despite the fact that differentiation of normal and abnormal behavior in this period is a challenge to reliable clinical identification (Campbell, 1995; DelCarmen-Wiggins & Carter, 2004; Wakschlag & Danis, 2009). Further, although these approaches specifically shied away from diagnostic methods due to their adevelopmental focus, this shift also led to an often disjunctive approach in which diagnostic methods were suddenly introduced at school age, making it difficult to map coherent clinical pathways across age periods.

Over the past decade, a plethora of diagnostic instruments for clinical assessment of young children has been developed and validated, including structured and semistructured parent report diagnostic interviews developed for use with young children or adapted from interviews with older children (see also Chapter 1 in volume 1). These measures include interviews such as the Diagnostic Infant and Preschool Assessment (Scheeringa & Haslett, 2010), the Diagnostic Interview of Children and Adolescents for Parents of Preschool and Young Children (Ezpeleta, de la Osa, Granero, Domenech, & Reich, 2011), the Diagnostic Interview Schedule for Children: Young Child (Lucas, Fisher, & Luby, 1998), the Kiddie Disruptive Behavior Disorders Schedule (KDBDS; Keenan & Wakschlag, 2004; Keenan et al., 2007), the Preschool Age Psychiatric Assessment (PAPA: Egger, Ascher, & Angold, 1999), and the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL) for the assessment of preschool children (Birmaher et al., 2009). The increased use of structured diagnostic interviews reflects a meaningful shift toward in-depth assessment of the intensity, frequency, duration, and contexts of behaviors relevant to psychopathology. For example, using data from the PAPA, Egger and Angold (2006) showed that applying ODD symptom frequency thresholds from older children to preschoolers results in significant overidentification, with 20–57% of preschoolers exhibiting common symptoms. The development and validation of clinical interviews in this age period is particularly advantageous in improving efforts to characterize the nature of emotional and behavioral problems in a developmentally sensitive manner. Further, many of these instruments incorporate some developmentally relevant information to enhance the relevance and quality of the assessment of psychopathology in young children (e.g., KDBDS, PAPA).

Reliability and Validity of Preschool Psychopathology

There is ample evidence to support the reliability and validity of psychopathology in young children, including data that suggest good interrater and test-retest reliability of diagnostic assessments, that rates found in young children are similar to those identified in older children, symptoms are associated with parent- and teacher-rated impairment, family history, observed behavior, later psychopathology, and response to empirically supported treatments.

First, there is evidence of interrater (e.g., Bufferd et al., 2011; Keenan et al., 2007; Wakschlag, Hill, et al., 2008) and test–retest (Egger, Erkanli, et al, 2006; Ezpeleta et al., 2011; Keenan et al., 2007; Wakschlag, Hill, et al., 2008) reliability in the use of diagnostic interviews and observations to assess psychopathology in young children. Regarding validity, rates of disorders identified in preschool-age children (e.g., Bufferd et al., 2011; Bufferd, Dougherty, Carlson, Rose, & Klein, 2012; Egger, Erkanli, et al, 2006; Lavigne et al., 2009) are generally similar to those found in epidemiological studies with school-age children and adolescents (Angold et al., 2012; Burstein

et al., 2011; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Froehlich et al., 2007; Merikangas et al., 2010). Second, a range of known correlates have been linked to psychopathology in young children including associations with (1) impairment in functioning across domains (e.g., with parents, siblings, peers, in preschool and day care) in a range of studies based on both parent and teacher report (Bufferd et al., 2011; Danzig et al., 2013; DuPaul, McGoey, Eckert, & VanBrakle, 2001; Egger, Erkanli, et al., 2006; Luby et al., 2002; Luby, Belden, Pautsch, Si, & Spitznagel, 2009; Wakschlag & Keenan, 2001); (2) family history of psychopathology (Bufferd et al., 2014; Dougherty, Smith, et al., 2013; Dougherty, Tolep, et al., 2013; Luby et al., 2002); and (3) standardized clinical observation (Bunte et al., 2013; Dougherty et al., 2011; Dougherty, Smith, et al., 2013; Wakschlag, Briggs-Gowan, et al., 2008). Third, psychopathology assessed in preschool-age samples persists in some children and predicts later psychopathology and impairment (Bufferd et al., 2012; Dougherty, Smith et al., 2015; Dougherty et al., 2015; Keenan et al., 2011; Kim-Cohen et al., 2009; Lavigne et al., 1998; Lavigne, Dahl, Gouze, Bryant, & Hopkins, 2014; Lee, Lahey, Owens, & Hinshaw, 2008; Luby, Gaffrey, Tillman, April & Belden, 2014; Riddle et al., 2013; Wakschlag, Briggs-Gowan, et al., 2008). Finally, although there are no known large-scale randomized controlled trials (RCTs) of psychological treatments for preschool psychopathology, several well-conducted studies (including some small-scale RCTs) suggest that empirically supported treatments can be applied effectively (Axelrad, Butler, Dempsey, & Chapman, 2013; Chronis-Tuscano et al., 2015; Hirshfeld-Becker et al., 2010; Lenze, Pautsch, & Luby, 2011; Rapee, 2013; Riddle et al., 2013; Sonuga-Barke, Thompson, Abikoff, Klein & Brotman, 2006).

Despite evidence for the validity of preschool psychopathology, questions remain about the developmental appropriateness of some *DSM* symptoms in young children (Egger & Angold, 2006; Keenan & Wakschlag, 2002). Although some diagnostic instruments attempt to include age-appropriate manifestations of psychopathology (e.g., KDBDS; PAPA) and some researchers apply modified criteria to the assessment of disorders in preschool children (e.g., relaxing the requirement for persistent mood difficulties and adding suicidal/death themes in play for a depression diagnosis (Luby et al., 2002); modifications to some DBD items (Wakschlag, Hill, et al., 2008)), some diagnostic categories include developmentally impossible or improbable symptoms. As mentioned above, many symptoms of CD are very unlikely to apply to young children (e.g., use of weapons, forced sexual activity, theft, truancy). Even if a few extreme children engage in these behaviors, these behaviors do not meaningfully characterize developmental differentiation of behaviors along the latent domain of concern for others and internalization of norms and standards that CD represents (that is, the symptoms reflect behaviors of adolescent boys; Carter, Gray, Baillargeon & Wakschlag, 2013; Wakschlag, Tolan, & Leventhal, 2010). This issue is relevant to other diagnostic categories as well; for example, Lahey and colleagues' (2005) work suggests that the inattentive type of ADHD is not particularly stable from preschool through elementary school age. This may be due, in part, to the developmental inappropriateness of ADHD inattention symptoms which focus largely on school-based skills and sustained mental effort, which do not capture the central features of developmental expression of normative regulation of attention in young children (Chacko, Wakschlag, Hill, Danis, & Espy, 2009). In addition, some cognitive symptoms of anxiety and depression are less developmentally probable in early childhood, such as excessive anxious apprehension about future events and rumination about past events. Finally, it is unclear whether the display of some behaviors (e.g., a preschool-age child assaulting a peer with a toy) reflects the same clinical meaning as an older child's behavior (e.g., an adolescent assaulting a peer with a weapon; Keenan & Wakschlag, 2000). Further, emphasis on these extreme and rare behaviors misses the boat in terms of capturing manifestations of aggression that qualitatively distinguish typical from atypical in this age period such as mild aggression in response to peer conflict versus hostile, intense aggression with intent to hurt (Wakschlag et al., 2010).

Measurement Gaps in the Traditional Categorical *DSM*-Based Approach: Where Do We Go From Here?

These measurement advances described above have had a profound impact on the nature of the discourse about preschool psychopathology, changing the focus of scientific inquiry from the earlier focus on whether psychopathology exists to the current emphasis on defining developmental phenotypes, sharpening early identification, and establishing links to specific mechanisms. Additional work is needed to further our understanding of the variation in behavior that pertains to the development of early-emerging psychopathology. First, in a diagnostic interview, the typical goal of each question is to establish whether a child meets a criterion for a particular disorder. However, in this process of rating whether a behavior crosses the criterion threshold, only more extreme forms of behavior are captured;

therefore, potentially clinically relevant information may be lost, particularly in the preschool period when many symptoms overlap substantially with normative misbehaviors and variation. That is, behaviors are only rated categorically as absent or present (or, in some cases, present in varying degrees of severity) whereas behaviors that fall short of the threshold, yet may still be pertinent, are considered absent. This issue is especially problematic for identifying prodromal signs of emerging psychopathology in young children as early identification and prevention can ameliorate chronic and persistent mental disorder trajectories more effectively than treatment once there is frank disorder (Insel, 2009). This limitation is consistent with criticisms of categorical classification in that it highlights the value of assessing the severity and frequency of the full spectrum of behavior from normative variation to clinical problems rather than relying on the presence or absence of a particular behavior (Arend, Lavigne, Rosenbaum, Binns & Kaufer Christoffel, 1996; Carter et al., 2013; Cole, Luby, & Sullivan, 2008; Wakschlag, Briggs-Gowan, et al., 2014). Although dimensional approaches are receiving increasing prominence across the life span, this issue is especially salient during early childhood when the critical clinical distinction is not *whether* the child engages in the behavior but *how*.

In addition, empirically based guidelines for determining when the intensity and frequency of young children's behavior are clinically significant are lacking. Cutoffs for symptom thresholds are not typically empirically derived, nor are there sufficient data to operationally define *DSM* terms included in diagnostic criteria such as recurrent, persistent, and excessive. Without such data, it is challenging to accurately determine whether a child exhibits clinically concerning levels of behavior compared to other children. Given that many defining features of common emotional and behavioral disorders are developmentally normative in this age period (e.g., moodiness, tantrums, short attention span; Gullone, 2000; Marks, 1987; Muris, Merckelbach, Mayer, & Meesters, 1998; Stringaris, 2011) and the high degree of noise in normative behavior, clear guidelines for identifying the actual signal of clinically salient behavior are needed.

Therefore, methods to detect developmental variation along the full spectrum relevant to psychopathology are essential as advances beyond the current method of symptom assessment that only captures severe behaviors. These methods can also identify developmental manifestations of psychopathology as they shift over time. Compared to more standard categorical approaches, a dimensional method of assessment can offer a more nuanced understanding of developmental course, better characterize heterogeneity of behavior, better incorporate information from various informants, and better delineate contextual factors that inform etiology. To do so, integration between developmental and clinical science is necessary such that specific developmental domains for characterizing the normal-abnormal spectrum are applied to the assessment of psychopathology in young children (Wakschlag, Briggs-Gowan, et al., 2014; Wakschlag et al., 2010).

MEASUREMENT ADVANCES: DIMENSIONAL OPERATIONALIZATION OF THE CONCEPTUALIZATION AND THEORY

There have been a number of advances in identifying the dimensions that constitute abnormal behavior, particularly in the area of DBDs. These advances include questionnaire, daily diary, and observational measures.

Questionnaire

We (Wakschlag, Briggs-Gowan, and colleagues) have developed a suite of novel assessment tools to sharpen differentiation of the normal–abnormal spectrum of behavior within the developmental context of early childhood, including both questionnaire and direct observation measures (Mian, Carter, Pine, Wakschlag & Briggs-Gowan, 2014; Petitclerc, Briggs-Gowan, Anderson, Burns & Wakschlag, 2014; Wakschlag, Hill, et al., 2008; Wakschlag, Briggs-Gowan, et al., 2008; Wakschlag, Briggs-Gowan, et al., 2014; see also Chapter 1 in volume 1). The unifying theme of these instruments is their goal of operationalizing features of behavior we have theorized as key to the normal–abnormal differentiation (i.e., quality, frequency and expectability in context; Wakschlag, Hill, et al., 2008; Wakschlag et al., 2010). The Multidimensional Assessment Profile of Disruptive Behavior[1] (MAP-DB) is a questionnaire measure that assesses four dimensions of behavior: temper loss, aggression, noncompliance, and low concern for others (with low concern composed of two subdimensions: disregard for others and punishment insensitivity) theorized to be defining features of disruptive behavior syndromes (Nichols et al., 2014; Wakschlag, Briggs-Gowan, et al., 2014). Reflecting a core principle of

[1]This instrument was originally called the Multidimensional Assessment of *Preschool* Disruptive Behavior but has since been renamed to reflect its use across broader age periods.

the developmental psychopathology approach (Cicchetti & Toth, 2009; Sroufe, 1997), each dimension is defined as a deviation from normative developmental processes of early childhood (for theoretical underpinnings see Wakschlag et al., 2010; Wakschlag, Henry, et al., 2012). For example, the temper loss dimension reflects problems in regulation of overt anger, including both temper tantrums and irritable mood. The regulation of negative emotion is a core developmental task of early childhood and reflects the capacity to modulate the intensity and temporal features of emotional arousal in a goal-oriented manner (Batum & Yagmurlu, 2007; Cole, Michel & Teti, 1994; Gilliom, Shaw, Beck, Schonberg & Lukon, 2002). Temper loss quality is assessed in terms of modulation of angry, irritable behavior from expectable (e.g., becomes frustrated easily) to highly dysregulated (e.g., tantrums until exhausted). Items assessing the developmental expectability of temper loss in context includes normative contexts (e.g., tantrums when tired, hungry, or sick) and tantrums that are not contextualized (i.e., out of the blue). An objective frequency scale is used to determine how often behaviors typically occur and when a behavior occurs at a frequency outside expectable levels, using a psychometric definition of atypicality (i.e., occurs in less than 5% of the population) (Wakschlag, Choi, et al., 2012). This had enabled us to establish that contrary to the terrible twos myth (i.e., that problem behaviors predominate in early childhood), normative misbehaviors are common but not frequent. This is consistent with the PAPA's approach to define abnormality as behaviors occurring at a frequency that is present in less than 10% of the sample (Egger, Kondo, & Angold, 2006). For example, data from the MAP-DB in two independent community samples of demographically diverse preschoolers (N = 3,373) showed that while 83% of preschoolers have tantrums regularly, less than 10% do so daily; a pattern robust to individual differences in child age, sex, ethnicity and poverty status (Wakschlag, Choi, et al., 2012; Wakschlag, Briggs-Gowan, et al., 2014). Similar frequency patterns were detected across the other behavioral dimensions, although the frequency at which a behavior becomes atypical varies by its severity (Wakschlag, Briggs-Gowan, et al., 2014). For example, being aggressive when frustrated is only atypical when it occurs most days of the week, whereas spitting and cursing are atypical even when they occur rarely.

While dimensional approaches have long been a hallmark of developmental psychopathology research (Achenbach, 1997), assessments have typically been counts of problem behaviors rather than characterization along an ordered spectrum. One novelty of the MAP-DB is the inclusion of both normative and problem behaviors to capture the full behavioral spectrum of expression. Using item response theory (IRT) methods, we have characterized the normal–abnormal spectrum for each dimension in a large community sample of preschoolers (Nichols et al., 2014; Wakschlag, Briggs-Gowan, et al., 2014). Behaviors are psychometrically ordered from normative, commonly occurring behaviors to severe, rarely occurring behaviors. Table 5.1 provides examples of behaviors across the severity spectrum for each of the MAP-DB Dimensions.

This psychometric, developmentally based approach is designed to provide an empirical foundation for clinical applications of dimensional approaches that conceptualize psychopathology as falling along a continuum rather than being defined by a single extreme threshold. Early individual differences along these dimensions are shaped through development into adaptive or maladaptive patterns, which at their extreme constitute mental disorders (Cicchetti & Richters, 1997). While there is increasing emphasis on integrating dimensional approaches that characterize the spectrum from normative variation to abnormal behavior into clinical classification (Helzer et al., 2008; Insel et al., 2010), empirically based approaches for their clinical application are underdeveloped. This is an especially important gap in early childhood, where capturing the full liability spectrum may increase sensitivity for capturing prodromal stages of risk.

To advance the clinical application of spectrum approaches to preschool psychopathology, we have recently

TABLE 5.1 Illustrative Behaviors Across Normal–Abnormal Dimensional Spectrum

Dimension	Mild	Moderate	Severe
Temper Loss	*Have a tantrum*	*Have difficulty calming down when angry*	*Hit/bite/kick during tantrum*
Aggression	*Aggressive to get something s/he wants*	*Pinch/scratch/pull hair*	*Hit/shove/kick nonparental adults*
Noncompliance	*Act stubborn*	*Disobey out of the blue*	*Automatically resist whatever you ask*
Low concern for others			
Disregard for others	*Not care about others' feelings when frustrated/angry/upset*	*Act like didn't care about pleasing others*	*Enjoy making others mad*
Punishment insensitivity	*Deny did something not allowed*	*Keep on misbehaving no matter what you do*	*Refuse to apologize*

Source: From Wakschlag, Briggs-Gowan, et al., 2014; Nichols et al., 2014.

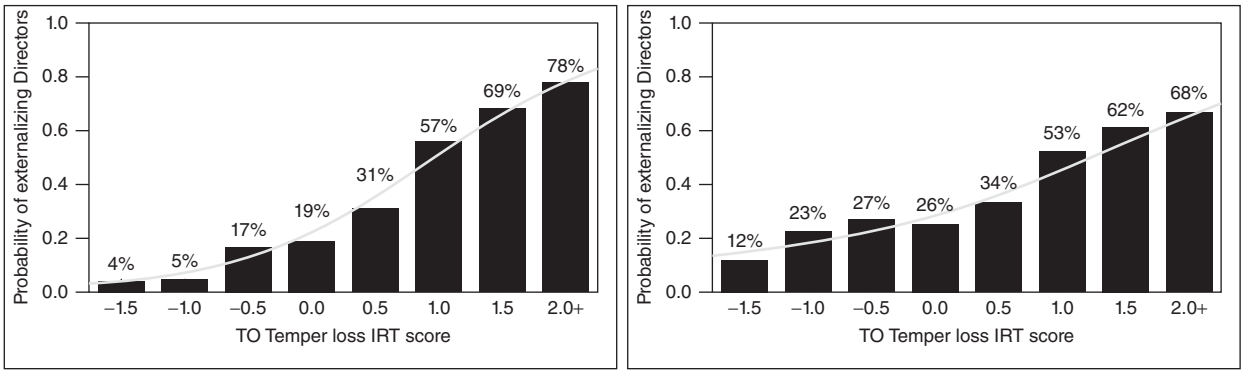


Figure 5.1 Relation of temper loss to externalizing disorders (left). Relation of temper loss to internalizing disorders (right). *Source:* Wakschlag, Estabrook, et al., 2014.

begun to examine the shape of the relation between the MAP-DB Temper Loss dimensions and clinical outcomes (Wakschlag, Estabrook, et al., 2014). In multivariate regression analyses, Temper Loss demonstrated a strong linear relation to probability of both externalizing and internalizing disorders (Figure 5.1), consistent with the cross-cutting nature of irritability in developmental psychopathology (Krieger, Leibenluft, Stringaris, & Polanczyk, 2013). For example, probability of externalizing disorder increases substantially as Temper Loss increases above the mean (Figure 5.1a). Importantly, this increased risk of disorder occurs at levels of Temper Loss typically considered to be normative. For example, children 1 standard deviation above the mean (typically considered at the upper bound of the normal range), had more than a 50% probability of an externalizing disorder. A similar, although less steep, linear trend was found for Temper Loss and internalizing disorders (Figure 5.1b). For continuous outcomes, a curvilinear pattern was found, such that a 1 standard deviation change at the lower end of the spectrum had little effect on level of clinical symptomatology, but this same level of change as children progressed along the dimensional continuum had a much larger impact (Wakschlag, Estabrook, et al., 2014). This dimensional approach to irritability assessment has also shown incremental utility in uncovering the neural substrates of irritability in young children (Perlman et al., 2014). For example, MAP-DB dimensional Temper Loss scores were associated with decreased activation of the anterior cingulate and striatum during a frustration task (Perlman et al., 2014).

Daily Diary

Compared with DBDs, relatively little attention has been devoted to characterizing the normal–abnormal spectrum of behavior relevant to internalizing problems such as anxiety, irritability, and sadness (Luby & Belden, 2006). Given that these problems can be identified in early childhood (Bufferd et al., 2011; Egger & Angold, 2006; Franz et al., 2013; Luby et al., 2002), persist over time (Bufferd et al., 2012; Luby et al., 2014) and that internalizing symptoms often reflect extreme displays of normative emotional processes in early childhood (e.g., separation anxiety, social fear; Gullone, 2000; Marks, 1987; Muris et al., 1998); irritability; Stringaris, 2011), it is essential to assess the severity and frequency of the full spectrum of behavior from normative variation to clinical problems, rather than assessing the presence or absence of behavior and identify the level of behavior that is associated with impaired functioning (Carter, Briggs-Gowan, & Davis, 2004; Eley et al., 2003). Improved developmental sensitivity of the assessment of children's emotions and behaviors can enhance the characterization of early-emerging psychopathology and refine intervention efforts to prevent or improve impairing developmental trajectories. To this end, we (Bufferd, Dougherty, & Olino, in preparation) have recently applied daily diary methodology in a novel manner to the assessment of behaviors relevant to anxiety and depression. In addition to beginning to document the typical range of behaviors displayed that may be clinically relevant, the daily diary methodology minimizes the biases introduced by retrospective recall required for parents to report about their children's behavior. Whereas most measures ask parents about their children's behavior in the previous month or so (up to three months or more), the daily diary requires parents to report about their child's behavior from that day. Ideally, a reduced recall period will diminish recall bias and enhance the accuracy of reports, which is essential in an endeavor that seeks to document the normative range of behavior and in which behaviors are frequently occurring. In addition, the daily diary provides a feasible method for obtaining objective

frequency of behavior rather than subjective frequency (e.g., asking parents to note whether children's behaviors occur sometimes, often, etc.), which, in some measures, relies on comparison to other children.

In a sample of 292 3–5-year-old children from two geographic regions (San Diego, CA and Washington, DC metro area) we asked primary caregivers to report about their children's daily behavior for 14 consecutive days, including the frequency, duration, and context of the behaviors. Items were derived from common anxiety problems in early childhood, including social anxiety and separation anxiety, as well as symptoms of depression. Items included behaviors such as distress when separating from a parent, somatic complaints, and social fear with other adults, children, and in new situations, and irritability, sadness, low interest or pleasure in activities, and sleep difficulties. In addition, each day, parents rated the extent to which each behavior was impairing (e.g., whether the behavior impacted the parent–child relationship that day) as well as provided overall ratings of impairment (extent of distress for the parent, the child, and the quality of the parent–child relationship from that day.

In a preliminary exploration of the anxiety and depressive behaviors, confirmatory factor analyses (CFA) tested dimensionality of the underlying separation anxiety, social anxiety, and depression dimensions. Both social anxiety and depression and, to a lesser extent, separation anxiety items assessed on a daily basis reflected coherent underlying dimensions. Using IRT analyses, we examined item characteristics with graded response models (GRM). Difficulty parameters reflected differential functioning across items such that some behaviors occurred less frequently than others to be severe (>95th percentile); for example, worry that a caregiver would get hurt or not return after being apart, worry about being left with another caregiver, shyness with familiar adults, avoidance of or withdrawal from social situations, low interest or pleasure, fatigue, and difficulty concentrating each had to occur at least three to four times over 14 days for the behavior to be considered severe; however, items such as distress when separation was anticipated from caregiver, fear about sleeping separately from the caregiver, shyness around new adults, sadness, and tearfulness were not severe at any frequency, suggesting that these behaviors are normative during this period of development.

The data from this study will provide preliminary evidence for the feasibility of a daily diary method to assess emotions and behaviors relevant to internalizing psychopathology in young children. In addition, the data begin to characterize the frequency of the spectrum of behavior from normative variation to clinical problems and will identify the level of daily behavior that is associated with impaired functioning. It is necessary to build on this study in future work with larger samples to more precisely document the parameters of the range of normative intensity, frequency, duration, and context of behaviors relevant to clinical risk in young children (Cole et al., 2008; Luby & Belden, 2006).

Observations

Drawing on robust findings that diagnostic observation, as exemplified in the Autism Diagnostic Observation Schedule (ADOS), adds precision for accurate early identification of autism (Lord, Leventhal, & Cook, 2001), we (Waskchlag, Briggs-Gowan, and colleagues) developed similar direct observation tools to aid in the differentiation of normative versus abnormal manifestations of disruptive behavior and anxiety in early childhood (Mian et al., 2014; Petitclerc et al., 2014; Wakschlag, Hill, et al., 2008). The Disruptive Behavior Diagnostic Observation Schedule (DB-DOS) uses presses designed to elicit differentiation of normative variation from clinically concerning behavior. Fundamentally, the goal of the DB-DOS is to tax the child's capacity for emotional and behavioral regulation during ecologically valid mild challenges (e.g., ease of elicitation and difficulty recovering from anger/irritability, intransigence of defiance); its conceptual developmental/clinical framework was the foundation for the MAP-DB. Behavior is rated along two domains: problems in anger modulation (akin to the MAP-DB temper loss scale) and problems in behavioral regulation (largely parallel to the MAP-DB noncompliance scale). Behavior is coded during interactions with parent and examiner along a clinical continuum ranging from normative variation to clinically concerning. Parameters of clinical concern include modulation, intensity, responsiveness to environmental support, and occurrence in developmentally unexpectable contexts. Observed behavior on the DB-DOS, particularly problems in behavioral regulation with the examiner, has demonstrated incremental utility for clinical differentiation and prediction of DBDs above and beyond parental report of DBD symptoms, and has also been used to predict ADHD (Bunte et al., 2013; Petitclerc et al., 2014; Wakschlag, Briggs-Gowan, et al., 2008). We also found sex differences in patterns such that disruptive boys' behavior is relatively stable across interactional contexts but disruptive girls show dramatic contextual differences—with high levels exhibited during interaction with their mothers but well-modulated

behavior during interactions with the examiner (Gray et al., 2012).

The Anxiety Dimensional Observation Scale (ANX-DOS) was developed along similar lines, although only a parent context has been validated to date (Briggs-Gowan et al., 2014; Mian et al., 2014). Here, presses are designed to elicit the full range of expression of fearfulness and anxiety (e.g., fear, arousal, startle, separation anxiety). The ANX-DOS builds on foundational work of behavioral inhibition paradigms (e.g., Kagan, Snidman, & Arcus, 1998; Rubin, 1989) but diverges from this approach by moving away from event-based coding (e.g., latency to touch) to capturing qualitative features of behavior that define the phenotype of anxious behavior in young children in a clinically and developmentally salient manner (see Chapter 1 in volume 1). In its early stages of validation, the ANX-DOS has demonstrated specificity in relation to neural substrates of anxiety (e.g., relation to attention bias to threat) not detectable based on parental report of anxiety, as well as incremental utility for clinical differentiation (Briggs-Gowan et al., 2014; Mian et al., 2014).

Thus, standardized clinical observations show promise for enhancing accurate identification of common emotional and behavioral problems of early childhood. This area is only beginning to be mined. One important next step is elucidation of where parent report and standardized observation converge and diverge in identification of clinically salient patterns and the correlates and prognostic differences between these groups (Shernoff, Hill, Danis, Leventhal, & Wakschlag, 2014). That is, which children are identified by both parent report and observation, which identified by only one source, and what does this mean for clinical progression? For example, one potential utility of the DB-DOS is its capacity to efficiently provide information about the cross-contextual pervasiveness of the child's disruptive behavior. Our findings suggest that behaviors displayed in the examiner context of the DB-DOS may serve as a proxy for patterns of behavior in real-world settings with nonparental adults (De Los Reyes, Henry, Tolan, & Wakschlag, 2009). Clinical observation may also be a particularly important informant when parental biases obscure accurate reporting if, for example, parental history of psychopathology colors their judgment of whether their children's behavior is problematic. Finally, with the recent advent of developmentally sensitive methods of all types, the field is now positioned to more rigorously test specific ways observation may be most useful. For example, we theorize that direct observation may be of greatest utility for children around the midpoint of the normal–abnormal dimensional spectrum. That is, it may be more straightforward to rely solely on informant reports for children at the extremes (i.e., with very well-regulated or highly dysregulated behavior). In contrast, milder, more intermittent or less pervasive types of problems are challenging for clinical decision making during this age period, when biases tend toward "watch and wait" with the assumption that these are transient normative misbehaviors. This conservative approach may constrain early identification in prodromal phases of psychopathology. For example, observed dysregulation on the DB-DOS differentiates preschoolers with a family history of bipolar disorder from those without, perhaps capturing children in the prodromal phase of risk (Tseng et al., 2015). As the field moves increasingly toward clinical applications of developmentally sensitive dimensional approaches (Wakschlag, Estabrook et al., 2014), a more robust knowledge base will importantly advance the science of early identification.

CROSS-CUTTING DEVELOPMENTAL DOMAIN-BASED APPROACH TO PRESCHOOL PSYCHOPATHOLOGY

Despite these important advances in developmentally based assessment of common emotional and behavioral problems, a framework for conceptualizing psychopathology in young children is still needed. In general, the current taxonomy does not include developmental terminology, age, and setting specifications, details about developmental variations in symptom manifestation, or information about how to consider deviations from normative developmental patterns. For example, we do not have guidelines for determining when normative variation and misbehaviors achieve clinical significance for behaviors such as tantrums and aggression for disruptive behavior, short attention span for ADHD, inhibited behavior toward others or fearfulness for anxiety syndromes, or irritable mood, feelings of guilt, or reduced interest or pleasure for depression. To better distinguish normative from problematic behaviors and identify when behaviors interfere with functioning and mastery of essential developmental tasks, we next delineate a developmental domain framework designed to advance clinical operationalization of the normal–abnormal spectrum of behavior in early childhood. This framework is consistent with both long-standing conceptualization of developmental psychopathology (Cicchetti, 1984; Cicchetti & Toth, 2009; Sroufe, 1979; Sroufe & Rutter 1984) as well as more recent neurodevelopmental approaches designed to promote a

brain-based clinical classification system (e.g., RDoC; Cuthbert & Insel, 2013; Franklin et al., 2015; Insel et al., 2010; Sanislow et al., 2010; Wakschlag et al., 2010) that consider psychopathology from a dimensional and transdiagnostic perspective of the full range of behaviors relevant to typical and atypical development.

We propose a set of domains to delineate psychopathology as deviations from normative developmental processes. These core developmental domains were selected with the following criteria in mind: (1) each domain reflects an area in which developmental acquisition of a particular capacity is a central task of the preschool period; (2) both high and low ends of the domain reflect possibly atypical or problematic levels of behavior; and (3) domains are broad, include multiple related facets (e.g., social, emotional, cognitive), and cross-cutting. Importantly, domains reflect dynamic, interrelated processes that are impacted by a range of factors, such as temperament, context, parental behavior, and culture. Further, although these domains reflect developmental tasks that are essential to acquire during the preschool period, these capacities are also necessary for subsequent development. Therefore, difficulty in these domains may reflect the presence of psychopathology during the preschool age or predict future psychopathology in subsequent developmental periods. Although we view the use of these domains as an important step toward enhancing the developmental sensitivity of preschool psychopathology research, this framework is intended as a heuristic rather than an exhaustive characterization. Specifically, the domains and related content (i.e., normative mis/behavior, clinical indicators, and impairment) proposed will require expansion and pruning over time as researchers further characterize the spectrum of behavior relevant to psychopathology. Although here articulated specifically for early childhood, this approach could be meaningfully applied across developmental periods (Carter et al., 2013; Gray & Wakschlag, in press).

Table 5.2 includes each domain, the key developmental tasks associated with the domain during the preschool period, normative variation in mis/behavior, and examples of atypical behavior at the extreme ends of the domain (i.e., clinical indicators). In addition, we propose examples of impairment associated with deficits across the domains. The four domains include: emotion regulation, self-control, social engagement, and internalization of rules and standards. These domains are proposed as a framework for capturing the full variation in behavior in a developmentally sensitive, comprehensive manner and contributing to the conceptual delineation of normal–abnormal boundaries. Of course empirical data are needed to verify or refine these boundaries via improved precision of identification and prediction, as well as targeted interventions at the early phase of the clinical pathway.

In this section, we explicate the salience of the normal–abnormal spectrum within each cross-cutting domain by linking it to a particular form of psychopathology (or syndromes or set of syndromes) as an exemplar. To illustrate each domain, we matched forms of psychopathology to a key corresponding developmental domain in which disruptions in acquisition of the developmental tasks in that domain is particularly relevant for phenotypic expression: (1) emotion regulation and depression; (2) self-control and ADHD; (3) social engagement and anxiety; and (4) internalization of rules and standards and DBDs. For each domain, we also highlight how extremes at both ends of expression may be atypical (e.g., under- and overinternalization of rules and standards for disruptive and depressive syndromes, respectively) and briefly mention the ways each domain applies to syndromes other than the exemplar in each category. Although for heuristic purposes we discuss these as distinct domains, they are clearly overlapping (e.g., emotion regulation has a significant self-control component).

Emotion Regulation: Typical and Atypical Patterns Exemplified in Depression

Emotion regulation reflects one of the essential developmental tasks of the preschool period that is relevant to the development of depression (Luby & Belden, 2006) and, as we describe in this chapter, other manifestations of psychopathology (Cicchetti, Ackerman & Izard, 1995; Cole & Deater-Deckard, 2009; Keenan, 2000). The development of basic emotions such as sadness, joy, and frustration in infancy and early childhood (Izard, Hembree, & Huebner, 1987; Lewis, Alessandri, & Sullivan, 1990; Tronick, 1989), as well as more complex emotions such as guilt and shame in the preschool period (Barrett, Zahn-Waxler & Cole, 1993; Eisenberg, 2000; Kochanska, Gross, Lin & Nichols, 2002; Parisette-Sparks, Bufferd, & Klein, in press; Thompson, Goodvin, & Meyer, 2006) contributes to the need for young children to express and regulate these emotional experiences. In particular, during this time period, preschool-age children build on regulation skills (ideally) acquired since birth that enable them to implement a range of strategies to evaluate and modulate (i.e., reduce, maintain, enhance) emotional arousal to pursue goals, coordinate and maintain social connection, adapt to stressful experiences, and preserve well-being (Campos,

TABLE 5.2 Illustrating the Normal–Abnormal Spectrum: Cross-Cutting Developmental Domains and Variation in Behavior in Preschool Psychopathology

Domain[1]	Key developmental task during preschool period	Normative variation in behavior	Atypical behavior at the extreme ends of the domain (examples)	Evidence of Impairment Across Domains
Emotion regulation	• Distress tolerance • Regulated emotional expression • Achieving emotional equilibrium • Use of emotion language • Flexibility: use of varied, increasingly complex strategies	• Mild temper tantrums when frustrated • Brief clinging to a caregiver when confronted with novelty • Use of temporary distraction when distressed • Some resistance to caregiver soothing • Mild sadness in response to an upsetting event • Intermittent boredom • Concern about parents' and own, well-being, safety, etc.	• Unpredictable, prolonged, or dysregulated temper tantrums • Frequent irritable mood • Persistent difficulty managing transitions • Persistently difficult to soothe • Separation distress does not abate with familiarity • Intrusive, unpleasant worry • Frequent withdrawal from distressing situations • Difficulty showing joy and deriving pleasure from activities	
Self-control	• Inhibitory control • Delay of gratification • Use of language/problem solving to negotiate • Goal-oriented, planful behavior • Executive functioning	• Reactive aggression to peer conflict • Some difficulty persisting on challenging tasks • Mild difficulty waiting • Impulsive in high motivation contexts	• Aggression as a predominant response to frustration • Disorganized, poorly modulated activity • Poor persistence • Limited ability to wait for desired object/event	• Child experiences distress • Disrupts family routines • Limits family activities • Limits peer activities (e.g., play dates, birthday parties) • Disrupts relationship between parents, parents and children, and siblings • Difficulty attending school/daycare • Poor school performance
Social engagement	• Reciprocal peer relationships • Social communication • Empathy	• Refusal to share • Mild selfishness when goals conflict with peers' • Intermittent solitary play • Difficulty approaching new children	• Provokes others/nasty • Disregards others feelings • Difficulty developing and maintaining friendships • Difficulty with social reciprocity/exchange • Persistent social reticence • Overly focused on internal experience	
Internalization of rules and standards	• Conscience development • Achieving autonomy: compliance balance	• Situational concern with fairness • Limit testing (e.g., breaks rules to push the limits) • Assertive noncompliance • Follows most authority figures' rules	• Blatant disregard • Proactive aggression • Intransigent defiance • Reflexive no • Overly compliant and unassertive • Rigid rule following	

[1] All domains reflect dynamic, interrelated processes that are impacted by temperament, context, parental behavior, culture, and other factors.

Mumme, Kermoian & Campos, 1994; Cole et al., 1994; Cole, Martin & Dennis, 2004; Kopp, 1982; Thompson, 1994). These strategies are impacted by cognitive, language, and social development, and include both individual (e.g., self-soothing, distraction) as well as socially mediated (e.g., parental soothing; peer request to play) attempts to manage internal and external affective experiences. In addition, emotion expressions and poor regulation may impact others' behavior to improve regulation (e.g., child sadness can elicit caregiver warmth; child guilt can elicit peer reassurance) (Cole et al., 2004). Further, emotion regulation is also moderated by social skills. For example, Rubin and colleagues (1995) found that preschool-age children who showed both poor regulation and worse social interaction skills were rated higher on internalizing problems than children with better regulation and interaction skills; poor emotion regulation also predicts later social incompetence (Denham et al., 2003).

In typical development, adaptive emotion regulation includes features such as distress tolerance, regulated emotional expression, achieving emotional equilibrium, use of emotion language, and flexible use of varied, increasingly

complex strategies. Although we know that poor regulation is associated with psychopathology in children (Cicchetti et al., 1995; Cole, Zahn-Waxler, Fox, Usher & Welsh, 1996; Lengua, 2002), less attention has been devoted to understanding problematic emotion regulation and depression (and other conditions) in young children.

In young children prone to increased sadness, irritability, shame, and guilt, and decreased joy and pleasure, deficits in the regulation of these experiences can increase risk for or accompany depression. These processes are consistent with temperament models of risk for depression that suggest that high levels of negative affect and low levels of positive affect and difficulty regulating these emotional states confer risk for depression (e.g., Clark & Watson, 1991; Lonigan, Phillips & Hooe, 2003). First, these children may be prone to displaying insufficient (e.g., low pleasure, proneness to boredom) or excessive (e.g., sadness, irritability) levels of these emotions. For example, preschool-age children identified as inexpressive during a negative mood induction were rated as having more depressed (and anxious) symptoms in 1st grade compared to the modulated and highly expressive groups of children (Cole et al., 1996). In laboratory observations, children with a depression diagnosis showed more dysphoria compared to children who did not meet criteria for a depression diagnosis (Dougherty et al., 2011); these children also displayed significantly lower levels of exuberance (e.g., pleasure, joy). These associations have been found to persist: children who displayed low laboratory-observed positive emotionality during the preschool period also displayed more helplessness and less positive information processing at age 7 (Hayden, Klein, Durbin, & Olino, 2006). Further, children with parental history of depression have been found to show more shame and guilt in a laboratory task than other children (Parisette-Sparks et al., in press), and in a study using children's narratives and parental report, shame and guilt were associated with depression (Luby, Belden, Sullivan, Hayen, McCadney, & Spitznagel, 2009). Finally, children who demonstrate excessive irritability are also at risk for depression (Dougherty, Smith, et al., 2013; Wiggins, Mitchell, Stringaris, & Leibenluft, 2014).

In addition, preschool aged children are tasked with the need to use increasingly flexible, complex strategies to regulate their emotional experience. For example, a typically developing child may initially require caregiver support to ameliorate sadness, but over time, develop increasing abilities to self-soothe, distract themselves, identify and express emotional states to solicit support appropriately, and engage in constructive problem-focused coping. When considering risk for depression, these strategies can serve to reduce the intensity and duration of negative emotional states (e.g., sadness, irritability, guilt, boredom) as well as increase and sustain positive emotional states (e.g., pleasure, enthusiasm, interest in activities) (Luby et al., 2004; 2006).

Luby and Belden (2006) propose a model of emotion reactivity curves to parse each feature of the process: emotion stimulus baseline, emotion arousal onset, emotion peak, emotional arousal offset, and return to baseline. They describe the various points in the curves where depressive responses may deviate from the optimal curve in which a youth can respond to an emotionally salient event in a reasonable amount of time, experience the peak of the emotion at an appropriate level of intensity, and return to a euthymic emotional baseline. This model has not been tested to our knowledge, but is consistent with empirical evidence that school-age children who reported difficulty regulating feelings of sadness were more likely to report depressive symptoms compared to other children with less difficulty (Zeman, Shipman, & Suveg, 2002), as well as related evidence that problematic regulation in preschool age reflects frequent (at least daily) and prolonged episodes of temper loss (Wakschlag, Choi, et al., 2012). Over time, children's difficulty flexibly applying a range of regulatory strategies can increase risk for depression. If, for example, a child primarily withdraws from distressing situations (e.g., sadness after exclusion from a game with peers; guilt after breaking a sibling's toy) rather than self-soothing and solving the problems associated with the situations, then this behavior will likely recur via negative reinforcement (i.e., withdrawal from the aversive situation relieves distress) and he or she may have difficulty learning effective coping strategies, gaining social skills, deriving pleasure from activities, and improving mood to reduce risk for depression. However, as discussed previously, there is a pressing need to define the parameters of the frequency, intensity, severity, and context of normative emotional experiences and regulatory strategies employed to more precisely understand the level at which young children's emotional expressions are clinically concerning (Cole et al., 2008; Luby & Belden, 2006). This work would chart the range of normative to problematic emotional development to improve the assessment of individual children's difficulties and risk for depression.

Difficulties with emotion regulation also apply to ADHD, anxiety, and DBDs.

ADHD

The interface of cognitive and emotional control have been suggested as contributing to ADHD phenotypes,

particularly in young children with high negative emotionality amplifying poor cognitive control (Martel, 2009). In fact, joint cognitive and emotion regulation deficits have been theorized to define the phenotype of chronic, preschool onset ADHD (Sonuga-Barke, Auerbach, Campbell, Daley, & Thompson, 2005).

Anxiety

Young children with anxiety have difficulty with emotion regulation. They tend to react negatively to stressful situations (e.g., excessive crying, anger, and distress when separated from caregiver; inhibition, avoidance, and withdrawal in distressing situations; frequent somatic complaints like stomach aches and headaches; difficulty being soothed) (e.g., Carthy, Horesh, Apter & Gross, 2010; Suveg & Zeman, 2004). Indeed, research suggests difficulties in emotion regulation represent a core feature of anxiety in early childhood (e.g., Henderson, 2010; Suveg & Zeman, 2004; Suveg, Morelen, Brewer & Thomassin, 2010). Moreover, high levels of temperamental reactivity in young children, such as behavioral inhibition, have been found to be associated with emotion dysregulation, particularly emotional hyper-reactivity and maladaptive regulatory behaviors (e.g., Carthy et al., 2010; Henderson, 2010; Suveg et al., 2010). More specifically, high temperamental reactivity may interfere with a child's ability to distinguish different emotions contributing to a poor understanding of one's own emotional experience, which is considered a critical component of adaptive emotional functioning (Baker, Holloway, Thomas, Thomas, & Owens, 2004). Additionally, high temperamental reactivity may negatively impact a child's ability to generate and engage in adaptive regulation strategies (e.g., reappraisal) to modulate his or her emotional experience (Carthy et al., 2010; Suveg et al., 2010). Quite plausibly, these difficulties in regulating emotion may also negatively impact peer interactions and contribute to reticence to engage with peers, as described above. Thus, in addition to the social engagement processes described below, emotion regulation may also mediate the association between high temperamental reactivity (e.g., behavioral inhibition) and anxiety in early childhood.

DBDs

Problems in emotion regulation are a defining feature of ODD including both tantrums and irritable mood (Wakschlag, Estabrook, et al., 2014). These include problems in modulation of angry mood, rapid escalation, ease of elicitation and difficulty recovering (Wakschlag, Choi, et al., 2012). In a very intriguing analysis of the features of tantrums that differentiate disruptive, depressed and typical children, Belden and colleagues (Belden, Thompson, & Luby, 2008) found that DBDs are more likely to have dysregulated tantrums that included violence and occurred with nonparental adults relative to children whereas the tantrums of depressed children were more likely to include self-harm. It has also been shown that chronic irritability at preschool age predicts ODD (as well as depression) at early school age after controlling for baseline disorders (Dougherty, Smith, et al., 2013). In fact, the overlapping feature of irritability across depression and disruptive behavior led to the proposal for *DSM* 5 of a disruptive mood dysregulation disorder (DMDD), which combines elements of both. We and others have recently demonstrated its validity at preschool age (Copeland, Angold, Costello, & Egger, 2013; Dougherty et al., 2014).

Self-control: Typical and Atypical Patterns Exemplified in ADHD

Self-control reflects the capacity to self-modulate and monitor behavior in response to shifting environmental cues and conditions even in the absence of external monitors (Vaughn, Kopp, & Krakow, 1984). We focus here particularly on a central aspect of self-control, i.e., cognitive control, including the capacity for planfulness, control of impulses, and delay of gratification (Calkins, 2007), a developmental domain of particular salience to ADHD. Alternately characterized by developmental and cognitive neuroscience literatures as effortful control and executive function respectively, these parallel cognitive control constructs refer to the capacity for control and regulation of automatic or prepotent responses including inhibitory control and working memory (Zhou, Chen, & Main, 2012). Cognitive control processes enable effective goal-directed behavior by directing attention toward contextually relevant, and away from contextually irrelevant, information, as well as the ability to modify behavior in response to situational contingencies. Infants can engage in sustained and selective attention by the age of 9 months (Ruff & Rothbart, 1996). Maturation of neural systems that subserve attention across early childhood, particularly the prefrontal cortex, enables the increased voluntary control of attention (e.g., orienting, redirecting and maintaining attention, which comes online toward the end of the first to second year of life (Calkins, 2007). This executive higher level control enables the young child to engage in goal-oriented behavior including prioritizing, resolving conflicting goals, and planning and generating behavioral sequences to achieve them (Ruff & Rothbart,

1996). More sophisticated capacity to regulate attention in high motivation contexts begins to emerge at the age of 2, develops rapidly, and is present at stable form by the end of the preschool years (Derryberry & Rothbart, 1997; Kochanska, Coy, & Murray, 2001). Developmental chains have been identified: for example, greater focused attention at 9 months predicts greater effortful control at 22 months, which in turn predicts better self-control at 33 months (Kochanska, Murray, & Harlan, 2000). When impulsive, in the moment behaviors are reigned in, the capacity of the child to attain future- and socially (rather than solely self-) oriented goals is expanded, including capacity for long-term gain with short term delay, and social rewards of conforming to expectations and deferring to others (Leerkes, Paradise, O'Brien, Calkins & Lange, 2008). The development and consolidation of inhibitory control across early childhood and delays in its acquisition is of particular salience to emergent ADHD during this period as inhibitory control involves the capacity to deliberately and effortfully inhibit prepotent behavioral responses and flexibly shift and focus attention (Ruff & Rothbart, 1996). When such responses cannot be inhibited despite threat of punishment or loss of reward, this is considered a deficit in inhibitory control (von Stauffenberg & Campbell, 2007).

From a developmental perspective, the key features of ADHD are all defined by deficits in self-control: inattentiveness characterized by problems organizing and persisting, overactivity as poorly modulated movement, and impulsiveness as acting without reflecting (Taylor & Sonuga-Barke, 2008). At preschool age, self-control deficits manifest as problems in inhibitory control are associated linearly with ADHD symptoms (Sonuga-Barke, Dalen, Daley, & Remington, 2002).

Important early work by Campbell demonstrated that early problems in self-control indicative of ADHD are evident as early as the toddler period (Campbell, 2002). Direct observation of hard-to-manage 2–3-year-old boys across a range of contexts revealed that they had frequent activity changes (often <2 minutes), distractibility, and impulsive responding (Campbell, Pierce, March, Ewing & Szumowski, 1994). Interestingly, the hard-to-manage children did not differ in absolute level of activity—rather it was the *quality* of this activity that differed (i.e., they were more often out of their seats and off-task); 30% of these children met criteria for ADHD at age 6, and this group had a high risk of showing persistent ADHD through adolescence (Pierce, Ewing, & Campbell, 1999). In addition, observed toddler attentional disengagement during free play, a behavioral indicator of unoccupied wandering during unstructured activities, predicted impulsivity at age 8 (Olson, Bates, Sandy, & Schilling, 2002). Deficits in self-control as defined by impaired inhibitory control have been demonstrated in multiple studies of preschool ADHD, and such deficits at preschool age also predict ADHD persistence (von Stauffenberg & Campbell, 2007). There is also some evidence that taking preschool-age inhibitory capacity and symptoms jointly into account enhances prediction of school age ADHD (von Stauffenberg & Campbell, 2007). Low levels of self-control at preschool-age also have long-lasting impact on functioning and mental health through adulthood (Moffitt et al., 2011). Early findings from interventions designed to promote self-control by facilitating brain growth and self-regulatory capacities during early childhood via cognitive enrichment games and training in metacognitive strategies have shown promising results, including sustained improvements in executive function and reduction in hyperactive/impulsive symptoms over a 1-year period (Halperin, Bedard, & Curchack-Lichtin, 2012).

The validity of preschool ADHD in broad terms is well established (Egger, Kondo et al., 2006). One of the primary challenges to differentiation of preschool onset ADHD from transient neurodevelopmental lags or normative variation is that *DSM* symptoms do a poor job of capturing developmental expression of self-control within this age period (Campbell, Halperin, & Sonuga-Barke, 2014). This issue may contribute to high rates of false positives reported for ADHD (Healey, Miller, Castelli, Marks & Halperin, 2008). Although preschool ADHD shows modest stability (Lahey, Pelham, Loney, Lee & Willcutt, 2005; Willoughby, Pek & Greenberg, 2012), preschoolers identified with ADHD are approximately as likely to remit as to persist (Sonuga-Barke et al., 2005; Willoughby et al., 2012). High rates of intraindividual variability are also evident early in development: e.g., 60.4% of boys who often fidgeted at 29 months were not often doing so at 17 months, and similar intraindividual variation is seen in reverse (from 17 to 29 months) (Baillargeon et al., 2007). Although many factors shape individual differences in course (Campbell et al., 2014), one possible explanatory factor for the high level of remittance is that the current ADHD nosology fails to distinguish normative variation and transient delays in the acquisition of self-control from the onset of atypical patterns that mark the onset of a clinical pathway. Intriguingly, for differentiation of normative variation and clinical indicators, in the Campbell et al. study mentioned above, a subgroup of the early hard-to-manage children were identified that showed catch-up in these areas over time so that their behavioral profiles more resembled those of the healthy controls

by age 6–9. This neurodevelopmental lag is consistent with more recent findings from neuroimaging studies at older ages, indicating that children with ADHD exhibit delayed trajectories of cortical development particularly in prefrontal regions important for control processes, and that remittance is linked to alignment with typical cortical growth trajectories (Shaw et al., 2007). Improved cognitive control across the preschool period is associated with diminution of problems over time for children who were hyperactive/impulsive at age 3, whereas poorer cognitive control is associated with increased severity of problems over time (Rajendran et al., 2013). Normative variation is substantial in the timing of skill acquisition; thus, defining the features of poor self-control that demarcate atypicality versus transient delays is important for sharpening precision of identification (Sonuga-Barke & Halperin, 2010). Enhancing accuracy of identification of early ADHD is of particular importance given concerns about escalating rates of prescribing psychotherapeutic medication in preschoolers (Zito et al., 2000).

This is supported by developmental analysis of *DSM* ADHD symptoms. Many of the hyperactive-impulsive symptoms are plagued by developmental *imprecision* because they do not specify the developmentally expectable levels of self-control and how deviations from these are defined; in addition, many of the inattentive symptoms are developmentally *inappropriate* because they focus on aspects of self-control that are not developmentally relevant at preschool age (Chacko et al., 2009). Developmental imprecision may explain the fact that preschool hyperactivity symptoms are common and occur in ~50% of preschool children (Egger, Kondo, et al., 2006; Egger & Angold, 2006; Smidts & Osterlann 2007), along the lines of the normative misbehaviors we have psychometrically identified for DBDs. For example, symptoms such as difficulty waiting turn, often fidgeting, often runs and climbs are all defining features of early childhood behavior reflecting the emergent self-control skills of this age period. In fact, several studies have shown that as many as 47% of preschoolers often interrupt and up to 72% are on the go (Egger, Kondo, et al., 2006; Pavuluri, Luk, & McGee, 1999; Smidts & Osterlann, 2007). In contrast, the emphasis of the inattention symptoms on sophisticated capacity for self-control expectable at older ages with particular emphasis on the demands of a school setting (e.g., often has trouble organizing tasks and activities, fails to finish schoolwork, chores or work, makes careless mistakes, avoids tasks requiring sustained mental effort) is out of step with the developmental capacities of preschool-age children (Chacko et al., 2009; Egger, Kondo, et al., 2006). Thus, it is not surprising that inattentive symptoms are less common at this age (Smidts & Osterlann, 2007).

Egger and colleagues have suggested that the use of psychometrically derived frequency cut-points specific to this age group may reduce over-pathologizing of variation in self-control as ADHD. They have also noted that while over-identification is likely at the symptom level in this age group (i.e., 1–2 symptoms are developmentally normative in 36.7% of preschoolers in the PAPA sample), having multiple ADHD symptoms is not normative (i.e., occurs <6% of preschoolers). While this addresses over-identification concerns to some extent, we postulate that developmental specification of ADHD symptoms will increase accuracy of identification, particularly as dimensional approaches gain more traction and identifying a spectrum of risk (rather than distinguishing extreme cases) becomes key. When behavioral indicators are defined in terms of age appropriate manifestations, more closely tied to developmental capacities for self-control, and empirically derived frequency parameters are available, this will bring much needed clarity to pediatric clinical decision making. This would mean characterizing ADHD symptoms at this age as problems of dyscontrol in reference to developmentally expectable tasks and capabilities in early childhood, e.g., difficulty controlling attention to relevant rules in 1:1 play activities, cannot control talking in situations where remaining quiet is expected (e.g., when being read to), and continues to interrupt during structured, developmentally engaging activities (Chacko et al., 2009).

Lack of attention to developmental considerations of pervasiveness and impairment in ADHD also makes it difficult to know when levels of self-control are consistent with clinical problems. For example, defining pervasiveness as occurring in two or more settings (with particular emphasis on the school setting) may constrain accurate identification of ADHD in early childhood because the social ecologies of young children differ from that of older children (Willoughby et al., 2012). In particular, not all young children attend a structured school setting, and may not have a second regular context in which the nature of the context would make these behaviors evident except in extreme cases. This may, at least partially, explain why many hyperactive/inattentive preschoolers do not demonstrate cross-situational impairment (Healey et al., 2008). Evidence from developmental studies indicates that preschoolers' attentional control varies widely depending on the demand characteristics of activities (Ruff, Capozzoli, & Weissberg, 1998), suggesting that cross-contextual

variation is important to take into account for determining clinical salience (Chacko et al., 2009). Further, early cross-contextual problems of hyperactivity and impulsiveness have been shown to mark a more persistent ADHD pattern (Campbell et al., 2014). On the PAPA, this issue is addressed by requiring that problems be present in at least two activities and that the child be unable to control the behaviors and not modulate them by admonition (Egger et al., 2006).

Halperin and colleagues suggested greater consideration of impairment as a method of differentiating normative variation in self-control from clinically salient problems reflective of preschool ADHD (Healey et al., 2008). They found that consideration of developmentally specified ADHD impairment criteria reduced the number of preschoolers identified as having ADHD by 46–77%. These findings are intriguing not only for ADHD but also for preschool psychopathology research more broadly, as impairment has received inadequate attention as a component of developmental specification.

Difficulties with self-control also apply to depression, anxiety, and DBDs.

Depression

Self-control involves tasks such as the use of goal-oriented behavior, attending to the full range of emotional experiences, and persistence in activities. Children with difficulty mastering these areas of development may display attention deficits in that they are overly attentive to the negative aspects of experiences (e.g., sadness, irritability, guilt) and ignore or minimize the positive aspects (e.g., low pleasure, low interest). In addition, children with poor self-control may easily withdraw from challenging situations. These self-control difficulties increase the likelihood of the development of depressive symptoms by reducing reinforcing opportunities for sustained, enjoyable activities that enhance self-worth and self-efficacy.

Anxiety

Preschool anxiety may also be associated with difficulties in self-control, which may manifest in anxious young children as deficits in attention shifting, overcontrol, and rigidity/inflexibility (Carver, 2005). Growing evidence indicates that children with a shy, inhibited temperament exhibit heightened attention biases to threat. As such, these children may display difficulties with flexibly shifting their attention from emotionally distressing stimuli, increasing risk for anxious symptoms (Briggs-Gowan et al., 2014; Pérez-Edgar et al., 2010, 2011). Similarly, high levels of inhibitory control (i.e., a child's ability to override a dominant response for a more appropriate response) have been shown to contribute to a shy, inhibited child's risk for anxiety, despite being an adaptive or protective factor for other young children at risk for conduct problems (Volbrecht & Goldsmith, 2010; White, McDermott, Degnan, Henderson & Fox, 2011). For instance, White and colleagues (2011) found that high levels of inhibitory control assessed at 48 months moderated the relationship between BI assessed at 24 months and anxiety during preschool age. Therefore, in conjunction with a heighted fear circuitry system, high inhibitory control may lead to overcontrolled, inflexible behaviors (e.g., excessive concern about making mistakes; poor persistence when faced with challenging tasks; avoidance of social situations; difficulty with transitions) in shy, inhibited children, thus elevating risk for anxiety (Volbrecht & Goldsmith, 2010; White et al., 2011).

DBDs

Preschoolers with DBDs have decrements in inhibitory control independent of ADHD (Shoemaker, Bunte, Wiebe, Espy & Dekovic, 2012). This is particularly true in motivational contexts (Shoemaker et al., 2012). Kochanska and colleagues have shown an interesting interaction effect of children's guilt (see internalization section below) and effortful control in predicting DBD trajectories (Kochanska, Barry, Jimenez, Hollatz & Woodard, 2009). For children observed to be guilt-prone across the toddler and preschool period (such as those with anxious or depressive tendencies), effortful control was unrelated to later DBDs. In contrast, toddlers observed to be low on guilt following transgression were protected from later DBDs if they had high effortful control (Kochanska et al., 2009). This interface across developmental domains highlights the complexity and multidetermined nature of early psychopathology trajectories (Cicchetti, 1984). They suggest that guilt may inhibit disruptive, rule-incompatible behavior via triggering of negative arousal for some children and promotes affective control to reduce this discomfort. Children who do not experience an aversive response to others' displeasure may be protected against later disruptive behavior via cognitive control that promotes restraint (Kochanska et al., 2009).

Social Engagement: Typical and Atypical Patterns Exemplified in Anxiety

Many development theorists argue that a key etiological factor contributing to the development of anxiety

in children is a shy or inhibited temperament style, which has been variously referred to as behavioral inhibition (BI), shyness, social reticence, and dysregulated fear (e.g., Kagan, 1997; Rapee & Spence, 2004; Rapee, Schniering, & Hudson, 2009). This temperamental style is characterized by long latencies to approach or communicate with unfamiliar people, onlooking or hovering behavior, the tendency to stay within close proximity of caregivers, and exhibiting signs of distress and withdrawal in reaction to novel contexts or challenging situations (Kagan, Reznick, Clarke, Snidman & Garcia-Coll, 1984; Rubin, Burgess, Coplan, 2002; Rubin, Burgess, Kennedy & Steward, 2003). Thus, differentiating a shy, inhibited temperament from anxiety disorders/symptoms is often challenging, as few studies have tested explanatory models of the nature of the relation between temperament and anxiety (Pagura, Cox & Enns, 2009) and these constructs share a number of similarities (Degnan, Almas, & Fox, 2010). For instance, several of the core features of BI (e.g., fearful affect, vigilance, social withdrawal) are also characteristic of several types of anxiety disorders (Degnan et al., 2010; Rapee & Coplan, 2010); however, only a subset of shy, inhibited children go on to develop an anxiety disorder (Fox, Henderson, Marshall, Nichols & Ghera, 2005). Nonetheless, research has consistently found that preschoolers' shy, inhibited, and withdrawn behaviors in response to social situations can indeed manifest as impairing anxious behaviors in early childhood (Biederman et al., 1990; Bosquet & Egeland, 2006; Coplan, Wilson, Frohlick & Zelenski, 2006; Henderson, Marshall, Fox & Rubin, 2004; Hirshfeld et al., 1992) and adolescence (Chronis-Tuscano et al., 2009; Schwartz, Snidman & Kagan, 1999).

The preschool years represent a period of dramatic advances in social engagement (i.e., child's involvement with peers), which is associated with age-related increases in social communication skills and empathy. During this stage, children are expected to transition from engaging in solitary or parallel play to more complex, interactive group play (Rubin, Coplan, Chen, Buskirk & Wojslawowicz, 2005). As such, the preschool years are often considered a sensitive period for the development of social communication skills required to initiate and sustain interactive and reciprocal peer relationships (Martin, Fabes, Hanish & Hollenstein, 2005). Examples of typical social communication skills during the preschool period include using verbal (e.g., using words to send a clear, direct message) and nonverbal (e.g., eye gaze, bodily gestures, facial expressions) behaviors to share ideas, problem-solve, and express one's needs; engaging in prosocial behavior (e.g., sharing, giving, helping); and demonstrating agreeableness (e.g., acquiescing to other's requests) and turn-taking (e.g., reciprocal role playing in fantasy play) (Rubin, Bukowski, & Parker, 2006). Additionally, in typical development, preschool children continue to expand their theory of mind and comprehension of others' emotions, desires, intentions, and beliefs that impact behavior (e.g., preschool-age children can comfort a peer who fell and hurt himself on the playground and can consider fairness in peer relationships) (Rubin et al., 2006). The accomplishment of these typical developmental tasks has implications for mental health, as the ability to flexibly navigate these social-emotional tasks can set the stage for healthy development, whereas deficits in these skills may place these children at risk for psychopathology. Below we describe how a shy, inhibited temperament or vulnerability to anxiety in early childhood might be associated with particular patterns of social engagement.

Although there is significant variation in expectable levels of social engagement in early childhood (e.g., behaviors such as occasional solitary play, initial hesitancy in approaching new peers, and refusal to share toys are to be expected), when these asocial activities predominate, they may reflect clinically significant anxiety that impairs expectable development of social engagement in this age period. As such, an inhibited, shy, and socially wary temperament style may become problematic and interfere with the development of adequate social communication skills and empathy necessary to initiate and maintain peer relationships, which in turn may contribute to clinically significant anxious symptoms (Rubin et al., 2005). For instance, children who display reticent behavior (e.g., watching other children from afar, remaining unoccupied during free play), rarely initiate contact, or retreat from social overtures from peers (e.g., demonstrate limited social reciprocity and exchanges) have fewer opportunities to practice and develop adaptive social communication skills and empathy. As such, these children may increasingly avoid age appropriate activities (e.g., play dates, birthday parties, playing with new peers at the playground) that they find anxiety-provoking and may be less appealing as a playmate to his or her peers (Ollendick & Hirshfeld-Becker, 2002). In fact, several studies have linked inhibited, shy temperament in preschoolers to greater social reticence and withdrawal in social settings and poorer social competence with peers (e.g., Bohlin, Hagekull, & Anderson, 2005; Coplan & Prakash, 2003; Henderson et al., 2004; LeMare & Rubin, 1987; Rubin et al., 2002). However, there is still much work to be done in the study of the relationship between social engagement and anxiety in

preschoolers to better identify those behaviors that are indicative of clinical concern, as well as those behaviors or factors that might facilitate new opportunities for social mastery (e.g., parents who use supportive strategies, such as encouragement, warmth, and support, to help their child explore and participate in social activities; having a best friend).

Difficulties with social engagement also apply to depression, ADHD, and DBDs.

Depression

Building on social development in infancy and toddlerhood that enables children to develop social skills, generate social expectations of others (typically based on interactions with caregivers), and use cues to interpret emotions related to the self and others (Baldwin & Moses, 1996; Tronick, 1989), preschoolers develop reciprocal peer relationships, improve social communication, and experience empathy for others. There are several ways these normative social processes may become problematic during the preschool period and confer risk for depression. Related to difficulties attending to the full range of emotions, when children are overly focused on their internal experiences and distress, their ability to meet others' needs, empathize, and engage in social reciprocity is compromised. Such children may, for example, be overly focused on feelings of sadness, loneliness, worthlessness, helplessness, or guilt. Children with these limitations are less appealing as playmates, which can reduce opportunities to develop social skills. In addition, such experiences may increase social withdrawal, further limiting social opportunities and worsening children's self-esteem (Hymel, Rubin, Rowden & Lemare, 1990; Rubin & Mills, 1988). Similar problematic social processes can occur in children prone to displaying excessive irritability and having difficulty maintaining friendships (Coplan & Armer, 2007; Rubin & Mills, 1988; Rubin et al., 2006).

ADHD

Social engagement of children with ADHD is also impaired, due in part to their difficulties with inattention and inhibiting responses in interactional contexts. Children with ADHD-related behavior have been found to be intrusive, over controlling and bossy, easily frustrated, transition frequently in play, have difficulty focusing one-on-one and in groups of peers, and understand social norms but cannot always modulate their behavior to conform to appropriate social standards (Alessandri, 1992; Barkley, 1997; Carpenter, Loo, Yang, Dang & Smalley, 2009; DuPaul et al., 2001; Guevremont & Dumas, 1994). More specifically, difficulties in attention may preclude a child from learning how to attend to social cues that are necessary for successful social interactions, whereas hyperactivity or impulsivity lead to inappropriate, annoying, disruptive behaviors in interactions. Thus, these behaviors are likely to dissuade peers from spending time with children with these difficulties, further reducing opportunities for the children to practice more appropriate behavior and enhance their social skills (Carpenter et al., 2009; Wheeler Maedgen & Carlson, 2000).

DBDs

Social inflexibility is a hallmark of preschool ODD including having a reflexive no, and stubborn resistance (Wakschlag & Danis, 2009). Young children with DBDs also have social information processing problems that bias them toward hostility in interpretations of social interactions (Coy, Speltz, DeKlyen & Jones, 2001). In addition, young children with callous traits have impaired eye contact during affectionate interactions with their mothers (Dadds et al., 2014).

Internalization of Rules and Standards: Typical and Atypical Patterns Exemplified in DBDs

The ability to act in accord with social standards and internally direct behavior accordingly is a hallmark of the acquisition of self-regulation in early childhood and is fundamental to adaptive socialization across the life span (Kochanska et al., 2001; Moffitt et al., 2011). From the infant-preschool period, the developmental progression of these behaviors shifts from externally regulated (in the presence of parent/caregiver) to internally motivated. Central to this domain is the early development of conscience articulated in seminal work by Kochanska as an internalized guidance system, with its two main components of self-regulated conduct (acting in accord with rules/standards) and moral emotions (feeling remorse or shame for violating rules/standards and concern about impact of behavior on others) (Kochanska & Aksan, 2006; Kochanska, Koenig, Barry, Kim & Yoon, 2010). Many intrinsic and extrinsic features influence the developmental acquisition of conscience (e.g., child cognitive and language capacity; the extent to which rules and standards are consistently conveyed and upheld by parents) but we here focus on the core intrinsic elements of conscience that undergird internalization of rules/standards of salience to psychopathologic patterns. In particular, we highlight atypicalities in compliance with rules and standards in

relation to ODD, and the development of moral emotions in relation to emergent conduct problems.

Compliance with Rules and Standards

Internalization of rules and standards necessitates child comprehension, mental representation of prohibitions, attentiveness to parental/environmental input, monitoring behavior, ability to shift behavior in response to environmental demands, inhibit behavior in response to both internal and external controls, generalize these principles across varying contexts, cognitively represent their consequences and enact the sequence of behavior associated with these rules/standards, and be motivated to uphold them (Forman, 2007). Early compliance with rules and standards occurs in the presence of an external regulator (Kochanska et al., 2001). Rudimentary capacities emerge very early in life, including the awareness of basic rules, modulation of behavior, and the ability to comply with demands by 12–18 months; the capacity to inhibit in the absence of external controls by 24 months, and the capacity to flexibly shift behavior and generalize rules and standards across varied situations and contexts by 36 months (Forman, 2007; Kochanska et al., 2001; Reznick, Morrow, Goldman, & Snyder, 2004).

Internalization reflects the autonomous owning of these standards by the child such that rule-compatible conduct occurs even in the absence of the caregiver, integrates a range of experiences, and is generalized (Forman, 2007; Kochanska et al., 2001). These internalized standards develop in tandem with the child's emerging sense of autonomy, such that noncompliance can be normative as it is neither desirable nor adaptive for children to rigidly adhere to rules and standards regardless of context or individual goals (Dix, Stewart, Gershoff, & Day, 2007). Thus, noncompliance is a normative misbehavior and commonly occurs in most children (Wakschlag et al., 2010). As compliance begins with directives or goals that are contrary to the child's goals, noncompliance actually increases from the toddler to the preschool period as part of burgeoning independence (Forman, 2007). Simple refusals, saying no without strong affect, and active negotiation and persuasion increase and are associated with positive developmental outcomes and contexts (Dix et al., 2007).

This presents a conundrum for the application of *DSM* ODD criteria at this age in a developmentally meaningful way. Noncompliance is a core feature of *DSM* ODD with symptoms such as often defiant, and often argues with adults (APA, 1994), which are often conceptualized as the beginning phase of antisocial behavior pathways (Loeber, Burke, Lahey, Winters, & Zera, 2000). The substantial evidence of the reliability and validity of *DSM-IV* ODD in preschoolers has importantly demonstrated that clinical levels of disruptive behavior can be differentiated even at this young age (Egger & Angold, 2006; Gadow & Nolan, 2002; Keenan & Wakschlag, 2004; Lavigne, Gouze, Bryant & Hopkins, 2014). Most recently parsed as a headstrong dimension derived from ODD symptoms (Stringaris & Goodman, 2009), noncompliance at preschool age has been shown to have distinct predictive utility and correlates relative to irritable ODD behaviors (Ezpeleta, Granero, de la Osa, Penelo, & Domenech, 2012; Stringaris & Goodman, 2009; Wakschlag, Choi, et al., 2012). However, such top down approaches (i.e., how do patterns in older children fit for early childhood) are limited for addressing the central problem of the developmental imprecision of ODD symptoms (Wakschlag, Leventhal, et al., 2007). For example, ODD headstrong symptoms, such as often defiant, argumentative are highly overlapping with normative misbehaviors. Further, *DSM* ODD is a conglomeration of heterogeneous behaviors that are not tied coherently to developmental domains, making it difficult to tie problematic behavior to specific atypicalities in developmental capacity (Wakschlag, Henry, et al., 2012). In addition, symptoms are determined by presence or absence rather than qualitative distinctions, which is problematic when the occurrence of a behavior is normative. Further, while preschool ODD substantially increases risk for later disorder, predictive accuracy is not strong (Bennett, Lipman, Racine, & Offord, 1998). While there is substantial stability in *inter*-individual differences over time, *intra*-individual stability is poor; for example, the majority of toddlers who exhibit frequent oppositional behaviors at age 17 months are not still doing so at 29 months (Baillargeon et al., 2007).

An emergent body of recent work that synthesizes developmental and clinical science has importantly advanced a developmentally informed understanding of noncompliance and features that demarcate the normal–abnormal spectrum based on the quality of compliance and noncompliance, the contexts in which it is elicited, and its frequency (Drabick, Strassberg, & Kees, 2001; Wakschlag, Briggs-Gowan, et al., 2007; Wakschlag, Henry, et al., 2012; Willoughby, Kupersmidt, & Bryant, 2001). Normative manifestations of noncompliance are goal directed, flexible, contextually expectable, and tempered by a desire to please others. In contrast, clinical manifestations are characterized by recalcitrant and dysregulated defiance and deliberate rule breaking. For example, differentiation of skillful (e.g., reasonable, calm) versus unskilled (e.g., dysregulated and confrontational) noncompliance in the

Response Style Questionnaire (RSQ) demonstrates that the same behavior (e.g., defiance) at preschool age may be adaptive or maladaptive depending on its quality (Drabick et al., 2001). When noncompliance is skillfully expressed, it is positively associated with social competence, whereas its unskillful expression is associated with disruptive behavior (Drabick et al., 2001). Adaptive noncompliance is assertive (i.e., goal directed, skillful, and socially engaged; Crockenberg & Litman, 1990; Drabick et al., 2001; Kuczynski & Kochanska, 1990). Observed quality of noncompliance (e.g., stubborn, pervasive and inflexible) during interactions with an examiner on the DB-DOS adds incremental utility to prediction of persistent disruptive behavior and impairment beyond *DSM* symptoms (Adjusted Odds Ratio = 4.53) (Wakschlag, Briggs-Gowan, et al., 2008). Observed rule-compatible conduct (with and without external regulation) across the toddler and preschool period is also associated with reduced risk of school age conduct problems (Kochanska et al., 2010).

To operationalize the full normal–abnormal spectrum of noncompliance, the MAP-DB includes a range of noncompliant behaviors that vary in terms of their developmental expectability (e.g., disobey when tired or frustrated vs. not do what you ask no matter what), provocativeness (e.g., show off or laugh while misbehaving), inflexibility (e.g., automatically resist whatever you ask) and context (e.g., with parent vs. other adults). Figure 5.2 shows the normal–abnormal spectrum of noncompliance, which was derived via IRT, a method that orders behavior along a severity continuum of a latent trait (Wakschlag, Briggs-Gowan, et al., 2014). As Figure 5.2 shows, theorized normative misbehaviors that occur in most children (e.g., acts stubborn) fall at the normal end of the spectrum, whereas behaviors theorized as pathognomonic (i.e., their occurrence per se is pathognomonic) fall at the severe end of the spectrum (e.g., do risky things he or she knew were not allowed).

We have theorized that high frequency is particularly important for determining developmental atypicality for normative misbehaviors, i.e., those in which most preschoolers engage, and less important for behaviors that are qualitatively pathognomonic (Wakschlag et al., 2010).

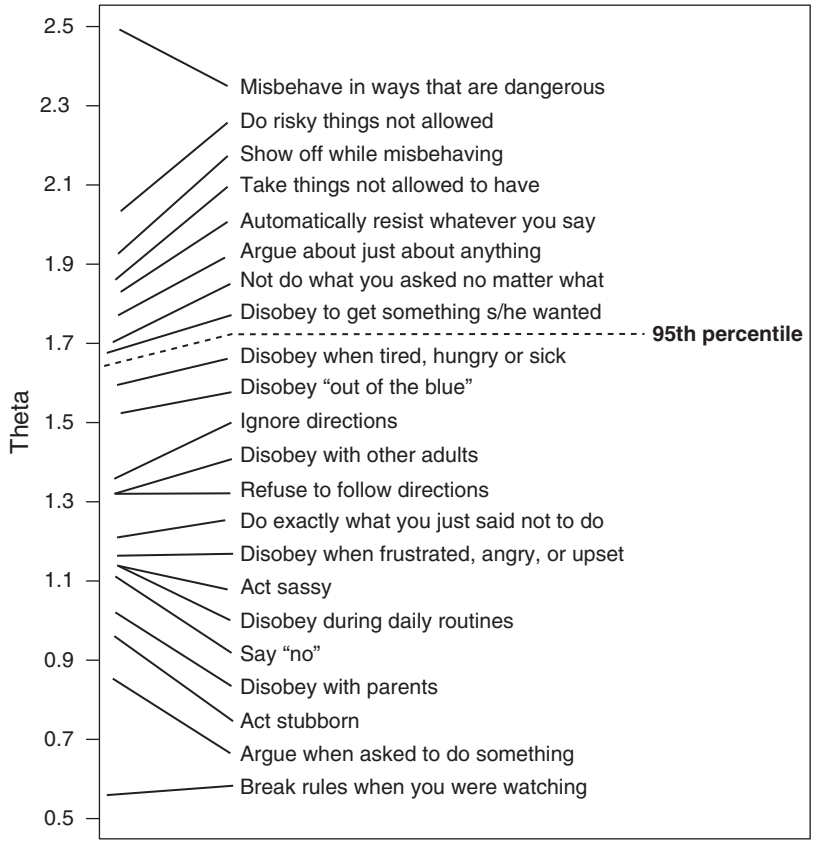


Figure 5.2 Normal–abnormal spectrum of MAP-DB noncompliance. *Source:* L. S. Wakschlag, M. J. Briggs-Gowan, S. W. Choi, S. R. Nichols, J. Kestler, J. L. Burns, . . . D. Henry, Advancing a multidimensional, developmental spectrum approach to preschool disruptive behavior, *Journal of the American Academy of Child and Adolescent Psychiatry, 53*, 82–89, 2014.

Questionnaires typically rely on subjective frequency ratings (never, sometimes, often) and *DSM* ODD symptoms also rest on occurrence of behavior such as defiance as often. The use of this approach has established that frequent occurrence of noncompliance is not normative. For example, population based studies indicate that <15% of toddlers often exhibit disregard for rules (recalcitrant noncompliance uncurbed by internal or external controls) and that doing so often across the early childhood period is atypical (Baillargeon, Sward, Keenan & Coa, 2011; Petitclerc, Boivin, Dionne, Zoccolillo & Tremblay, 2009). However, the absence of empirical parameters for determining how often is too often for normative misbehaviors leaves substantial room for error in clinical judgment and introduces a high level of informant bias (e.g., a lower tolerance for misbehavior would lead to lower threshold for what is considered often). The generation of empirically derived frequency thresholds is likely to be particularly informative for clinical decision making for those young children at the boundaries between normal and abnormal—where there is ambiguity about whether intervention is warranted. To generate empirically derived thresholds, we employed an objective frequency scale (ranging from never in the past month to many times per day) on the MAP-DB. This highlighted the variability in frequency patterns depending on the quality of the behavior. For example, normative expressions of noncompliance within developmentally expectable contexts (e.g., disobey during daily routines such as bedtime) occur regularly in 80% of preschoolers. In contrast, the exact opposite pattern is true for provocative forms of noncompliance (e.g., misbehave in ways that are dangerous or unsafe), which 80% of preschoolers are reported never to have exhibited over the past month. As a result, the frequency at which noncompliant behaviors becomes severe (i.e., occurs in <5% of the population) varies depending on their quality (Wakschlag, Briggs-Gowan, et al., 2014). This is consistent with prior work showing that frequency of noncompliance adds incremental utility for prediction of disruptive behavior for normative, but not qualitatively atypical, forms of noncompliance (Drabick et al., 2001).

Moral Emotions. Fundamental to internalization, is the experience of self-conscious emotions and aversive arousal following transgressions or distress caused to another, such as shame, guilt, discomfort, embarrassment, reparations in response to rule transgression, and empathic concern (Kim, Kochanska, Boldt, Nordling, & O'Bleness, 2014). It has been theorized that a key aspect of acquiring these complex emotions is the desire to please the caregiver that occurs within the context of a mutually responsive relationship (Grusec, Goodnow, & Kuczynski, 2000; Kochanska, Forman, Asksan & Dunbar, 2005). The expression of distress or discomfort following transgressions normatively emerges by the age of 2, building on emergent empathic capacities (Barrett et al., 1993; Chase-Lansdale, Wakschlag, & Brooks-Gunn, 1995; Kim et al., 2014).

Callousness, or the failure to experience such concern or remorse, is a core aspect of severe antisocial behavior as in CD, which in its most extreme form manifests as psychopathy (Blair, Mitchell, & Blair, 2005; Frick et al., 2003). We have suggested that the marked deficits in empathy, internalization and socio-moral function that mark this pathway can best be understood as *reduced responsiveness to socialization* with components of *low concern for others* and *punishment insensitivity* (Nichols et al., 2014). There is emergent evidence that low concern and callousness are evident at preschool age and have predictive utility for conduct problems (Ezpeleta, de la Osa, Granero, Penelo & Domenech, 2013; Hyde et al., 2013; Kimonis et al., 2006; Willoughby, Waschbusch, Moore & Propper, 2011; Wakschlag, Henry, et al., 2012). However, to our knowledge, no studies have yet linked low concern at preschool age to later severe antisocial behaviors or psychopathy.

On the MAP-DB, we have operationalized low concern for others and punishment insensitivity within a developmental framework. Developmental manifestations of low concern include not seeming to care about others' feelings and enjoy making others mad, and of punishment insensitivity include keep on misbehaving no matter what you do and refuse to apologize. Using IRT, both have demonstrated a severity spectrum for both domains (Nichols et al., 2014; Wakschlag, Briggs-Gowan, et al., 2014). While low concern varied along a severity dimension, all behaviors were pathognomonic, i.e., occurred rarely and exceeded a 95th percentile severity threshold. In contrast, punishment insensitivity included both common manifestations (act like s/he didn't hear you) and atypical manifestations (e.g., not care when punished and act like s/he did not know right from wrong), suggesting that punishment insensitivity is atypical when it predominates. Punishment insensitivity also demonstrated incremental utility for prediction of impairment over and above traditional disruptive behavior symptoms (Nichols et al., 2014). We have also demonstrated that preschool age punishment insensitivity is associated with concomitant impairments in reward learning that have been demonstrated in psychopathic adolescents and adults, suggesting that it might be an early indicator of this risk pathway (Briggs-Gowan et al., 2013; Dadds & Salmon, 2003). These findings suggest

that the defining features of CD are identifiable even at preschool age when they are defined in a developmentally meaningful way. However, as this type of developmental specification is relatively new, there is not yet a strong empirical knowledge base about its predictive utility for later CD and callous behaviors (Hyde et al., 2013). Using developmentally based paradigms, Kochanska and colleagues have shown that deficits in moral self observed during the toddler and preschool period predict later callous traits. For example, toddlers who did not exhibit tense discomfort and empathic concern during contrived mishaps, were more likely to exhibit school-age conduct problems (in interaction with parent–child relationship quality; Kim et al., 2014; Kochanska et al., 2010).

Difficulties with internalization of rules and standards also apply to depression, ADHD, and anxiety:

Depression

Preschoolers' increasing ability to engage in internalization of rules and standards reflects typical development during this period (Cole et al., 2008). For example, during the preschool period, children can evaluate their sense of self, empathize with others, and understand social and moral standards (Denham, 2007; Eisenberg, Spinrad, & Sadovsky, 2006; Muris & Meesters, 2014). Further, when children engage in misbehavior that disrupts others' well-being, they may show normative guilt and shame responses and can build on skills typically learned in toddlerhood such as repairing transgressions, confessing their role in the problem, and feeling temporarily badly about oneself (Barrett et al., 1993; Cole, Barrett & Zahn-Waxler, 1992; Kochanska, DeVet, Goldman, Murray, & Putnam, 1994). These skills enable empathy of others' distress and contribute to prosocial behaviors that repair transgressions.

However, some children show excessive and dysfunctional guilt and shame reactions to transgressions (Luby, Belden, Sullivan, et al., 2009). These reactions may include responses such as inaccurately blaming oneself for others' transgressions, feeling guilty/ashamed about a behavior long after the behavior occurred, and engaging in excessive apologizing or reassurance seeking in an attempt to relieve distress associated with the behavior. Consistent with themes described above, these behaviors likely increase negative self-focus, which can limit empathy toward others and interfere with reparative problem solving behavior (Eisenberg, McCreath, & Ahn, 1988; Eisenberg & Fabes, 1990), further worsening self-image and risk for depression. Girls may be more likely to display these behaviors compared to boys as suggested by recent findings (Luby, Belden, Pautsch, et al., 2009) and related to evidence that such internalizing emotions are likely to be differentially socialized by parents and teachers for girls compared to boys (Crick & Zahn–Waxler, 2003). Luby and colleagues (Luby, Belden, Sullivan, et al., 2009) suggested that such behavior may reflect that children are stewing in their negative emotion, particularly feelings of guilt and shame, and that this difficulty regulating emotional processes should be a target of intervention.

In addition, although children at risk for DBDs have difficulty following rules and social/moral standards, children at risk for depression may be apt to *overly* internalize rules and standards. For example, preschoolers of depressed mothers do not show age expectable increases in noncompliance (Dix et al., 2007). These children may show behaviors such as excessive compliance or following all rules without question or protest. Although these behaviors are normative in some cultures, Western cultures typically value children's assertion of their needs and shift toward increasing independence. Children who comply with rules and standards regardless of personal needs or preferences may be viewed as well-behaved and easy to manage by parents and teachers, further reinforcing the behavior. However, it is possible that these children are learning that their needs are not worthy of expression or attention, thus increasing their risk for depression.

ADHD

Internalization of rules and standards may also be deficient due to a range of cognitive control problems that interfere with holding rules in mind (working memory) and difficulty inhibiting without external surveillance. Impulsivity may interfere with children's abiding by rules even if they know them and want to keep them (Callender, Olson, Kerr & Sameroff, 2010). During laboratory observations of preschoolers' cheating behavior designed to differentiate normative from atypical cheating patterns, children observed to cheat without restraint and to display inappropriate positive affect while doing so were more impulsive and more likely to demonstrate later externalizing problems (Callender et al., 2010). Preschoolers with poor attention regulation have also been shown to display less empathic responding to peer distress (Eisenberg & Fabes, 1995).

Anxiety

In conjunction with high levels of inhibitory control, anxious preschoolers may be prone to over-internalizing rules and standards. Kochanska (1991, 1993) purports that a fearful temperament or vulnerability to anxiety in

early childhood may facilitate to the development of moral conscience and the internalization of rules and standards. More specifically, temperamentally fearful children may be less likely to engage in rule-breaking behavior because they are more likely to experience affective discomfort, such as shame, guilt, or worry, when they are criticized or commit a transgression (Kochanska, 1991, 1993; Kochanska, et al., 1994). Although this proneness to guilt may serve as a protective factor for some children, in its dysfunctional form, young children with a vulnerability to fearfulness or anxiety may be especially likely to develop excessive guilt and self-blame, which negatively impacts their self-efficacy and self-worth, and may contribute to their being overly compliant and unassertive in relationships. Likewise, an overinternalization of rules and standards may also lead to inflexibility and poor problem solving when faced with challenging situations, further exacerbating a child's anxiety symptoms.

TRANSLATIONAL APPLICATION OF DEVELOPMENTALLY SENSITIVE ASSESSMENT

Unquestionably, the momentum toward dimensional, developmentally specified approaches will enhance precision of clinical characterization. This is particularly true in the area of preschool psychopathology because the overlap of normative misbehavior and high levels of normative variation make reliance on categorical approaches that define atypicality based on frequency of extreme behaviors especially problematic. The many recent strides we have described above have substantially advanced developmentally sensitive methods in the dimensional characterization of early emerging psychopathology within a research context. However, their clinical application as a means of enhancing early identification is in its infancy (Wakschlag, Estabrook et al., 2014).

In particular, three steps are critical to moving dimensional, developmentally sensitive measurement from research use to clinical application for preschool psychopathology:

1. **Conduct empirical studies to systematically test whether developmentally sensitive approaches enhance accuracy of early identification.** We and others have theorized that developmentally sensitive measurement will reduce over- and underidentification by more accurately differentiating normative variation from clinical problems (Wakschlag & Danis, 2009). However, this theory has not been put to the test! Although measures such as the PAPA (Egger, Erkanli, et al., 2006; Egger et al., 1999) and the DB-DOS (Petitclerc et al., 2014; Wakschlag, Hill, et al., 2008; Wakschlag, Briggs-Gowan, et al., 2008) have demonstrated reliability and validity, the incremental improvement provided by their use for clinical differentiation has not been tested. An empirical knowledge base in this area is crucial for justifying the likely changes in nosology and one-size-fits-all approach that would ensue. For example, a number of studies using *DSM* diagnoses have shown that ~50% of children remit over a 6-month to 3-year period (Bufferd et al., 2012; Keenan et al., 2011; Kim-Cohen et al., 2005; Wakschlag, Briggs-Gowan et al., 2008). Does the use of developmentally sensitive measurement identify a group of children with more stable difficulties? Further, does the measurement identify young children with milder or variable difficulties or developmentally specific expressions who would not have been captured using traditional, adevelopmental approaches? These questions require longitudinal assessment and a thoughtful approach to assessing impairment given that the use of later diagnosis as outcome would be circular and would not necessarily offer more information than the current standard approach. For example, in keeping with recent modeling of the structure of preschool psychopathology (Olino, Dougherty, Bufferd, Carlson, & Klein, 2014), *a dimensional latent clinical risk factor* could be generated that would be composed of a higher order severity factor and two lower order latent factors: (1) a clinical symptoms factor, derived from symptom interviews and dimensional assessments on broad clinical domains (e.g., mood regulation, behavioral regulation); and (2) an impairment factor, across three impairment domains: family, social, and functional. This approach could be used to capture overall clinical severity as well as domain-specific patterns. Frequent and intensive longitudinal assessments that include retrospective and real time measures would be important to characterize the ebb and flow of these patterns over time. This is because typical annual assessments often miss a great deal of variation that occurs in between the end points, which may importantly inform understanding of who persists.
2. **Develop algorithms for integrating multimethod approaches into clinical decision making.** We now have a range of methods that have been specifically developed for preschool age assessment including clinical interviews, clinical observation, and dimensional questionnaires. Each of these measures provides a unique

source of information and error. Researchers and clinicians need to identify how various instruments can be best used in clinical practice. For example, there is evidence that the MAP-DB (Nichols et al., 2014; Wakschlag, Briggs-Gowan et al., 2014), DB-DOS (Petitclerc et al., 2014; Wakschlag, Hill et al., 2008; Wakschlag, Briggs-Gowan et al., 2008), and PAPA (Egger et al., 1999) identify early emerging disruptive behavior problems in a developmentally sensitive manner via parental report along multiple dimensions of children's behavior (MAP-DB), observation of behavior (DB-DOS), and interviewer-rated behaviors relevant to clinical diagnoses (PAPA). This multimethod, multiinformant approach would capture various dimensions relevant to psychopathology, offer specific details about the nature of the full range of behaviors, and generate traditional *DSM* diagnoses often required for reimbursement in clinical practice. However, the extent to which these developmentally sensitive measures provide convergent and divergent information remains unclear. Given the challenges of normative:atypical differentiation in early childhood, developing methods for combining these sources of information will undoubtedly enhance early identification. A first step toward this direction would be determining overlap and divergence across these methods and clinical profiles of children who are captured by one but not another method (see for example Kraemer et al., 2003; Risi et al., 2006).

3. **An algorithm that guides mental health clinicians in their use of a developmentally sensitive suite of assessment methods.** To do so, this approach must (1) be feasible for use in practice such that clinicians can access the measures, receive training in the administration and scoring, and incorporate the approach into real-world assessment and treatment planning; (2) provide added value over existing methods (e.g., symptom checklists, clinical interviews) by yielding information that is sufficiently sensitive, specific, and predictive of qualities such as treatment response and future behavior; and (3) capture varying developmental manifestations of latent qualities over time as challenges, competencies, and associated risk shift with age and experiences (Carter et al., 2013; Rutter & Sroufe, 2000; Rutter et al., 2006; Wakschlag, Leventhal, et al., 2007). Given that current assessment methods likely identify children displaying extreme behaviors quite well, this approach would be particularly beneficial for identifying children whose current behaviors are not extreme but are red flags for later clinical risk. Capturing such children in the gray area of behavior is essential for improving efforts to identify prodromal risk, and is particularly well-suited to the use of low-risk interventions (e.g., those that enhance developmental capacities described above such as emotion regulation and self-control versus more intensive pharmaceutical interventions).
4. **Develop a dimensional continuum for treatment decision making and test its effectiveness for improving outcomes.** The strength of these approaches (i.e., that they capture behaviors along a more natural spectrum and do not falsely dichotomize them as present or absent) is also their challenge. That is, because dimensional approaches do not provide clear thresholds for determining clinical significance, it is difficult to know how to incorporate them into clinical decision making. We would suggest a dimensional continuum of clinical decision that incorporates longitudinal assessment. Taking longitudinal change into account is at the heart of characterizing psychopathology within a developmental context and is particularly crucial for effective clinical use of dimensional approaches. Young children can vary within the normative range, within the abnormal range, and jump between these ranges over relatively short periods of time, and this variation predicts outcomes. Approximately one-third of children vary on dimensional scores by one standard deviation (SD) or more when longitudinal dimensional assessments are employed (Wakschlag, Estabrook et al., 2014). By accounting for the noise of transient events and the change reflecting developmental growth, longitudinal, dimensional assessment will provide key information for sharpening the distinction between normative variation and abnormal patterns. This would include empirically establishing the optimal number of time-points and intervals between them that will provide an adequate level of certainty and is also clinically feasible. Ideally, longitudinal assessment of all young children would precede clinical decision making except in the most extreme of cases where behavior is dangerous or severely impairing. In light of the high rates of stimulant medication to treat ADHD in preschoolers and concerns about overmedication, this might be an ideal domain with which to test such an approach.

   Below is an example of this type of approach:

Level 1: Well-regulated emotions and behavior

Level 2: Watch (longitudinally) and wait: clinically at risk

This level would be targeted to children with mildly elevated scores along a single dimension (e.g., .5–1 SD from the mean) to assess whether patterns escalate, remain

stable, or diminish. Clinical parameters could be empirically established; for example: preschoolers with scores within this range at three time points within a six month period are clinically at risk and warrant intervention.

Level 3: Low intensity intervention: clinically prodromal

For children with moderately elevated scores (>1 SD above the mean) in at least two domains.

Interventions that are low intensity or cost, and are developmentally promotive (e.g., improving self-regulation skills) may be warranted for young children at this level who have a 50% or greater chance of clinical disorder (e.g., 1 SD above the mean, Wakschlag, Briggs-Gowan, et al., 2014) as the benefits of preventing frank disorder are likely to far outweigh the costs of intervention.

Level 4: Treatment: clinically significant

Children with highly elevated scores (e.g., >2 SD above the mean) in at least two domains are clearly showing signs of atypicality that warrant treatment.

Despite the potential utility of the development of this type of approach for clinicians to employ to improve their assessment of early emerging psychopathology, many families more frequently encounter pediatricians or family physicians than specialty mental health providers, and parents may be more likely to express concerns about their young children's behavior in medical versus mental health settings. Therefore, an approach that capitalizes on these opportunities is essential. Often, parents' concerns reflect developmentally typical behaviors, and a pediatrician is tasked with the need to (often briefly) assess the behavior, its frequency, duration, and persistence, and the extent to which the behavior causes the child distress and interferes with family and peer relations. Wakschlag and colleagues (Wakschlag, Choi, et al., 2012; Wakschlag, Briggs-Gowan, et al., 2014) have mapped the dimensions of disruptive behaviors, and this work can be translated for use in pediatric practice to offer guidelines for the levels at which normative behaviors may connote risk. For example, they identified that although temper tantrums were normative in young children, tantrums that occurred unexpectedly or daily were rare; when persistent, such behaviors could warrant clinical attention. It is essential to generate similar information for behavior relevant to anxiety and depression; the research program described above that makes use of a daily diary approach will provide these data. Further, the use of computer adaptive test (CAT) approaches for incorporating preschool behavioral and socioemotional assessment into pediatric practice may be particularly useful because they are brief and efficient to administer (Choi, Reise, Pilkonis, Hays, & Cella, 2010; Wakschlag, Estabrook et al., 2014). Of course, guidelines for their interpretation and action steps would need to be well delineated. This type of concrete and concise information that can be feasibly conveyed to practitioners who frequently encounter young children and their families to guide decision making for services is essential in translating early psychopathology research into clinical practice.

In summary, foundational validation of preschool psychopathology has led to a proliferation of developmentally sensitive methods for its assessment. Our charge for the next decade is to ensure that empirical investigations focus on standardized methods for their clinical application and use. This work should importantly contribute to a more developmentally based, sensitive, and specific framework for the identification and treatment of preschool psychopathology.

CONCLUSIONS AND FUTURE DIRECTIONS

As described in this chapter, we have summarized clear evidence that symptoms and syndromes of psychopathology can be identified in a reliable and valid manner in early childhood. These difficulties have been found to be associated with impairment that impacts the child and family, and often persist into later development. Early identification and intervention are essential given that 1) earlier onset of psychological difficulties may contribute to greater long-term impairment and chronicity than later onset (Weissman et al., 1999), 2) early childhood offers a window for prevention or early intervention before school entry (Anticich, Barrett, Silverman, Lacherez & Gillies, 2013; Chronis-Tuscano et al., 2015; Kennedy, Rapee & Edwards, 2009; Lau & Rapee, 2011; Luby, Lenze & Tillman, 2012; Njoroge & Yang, 2012; Pincus, Eyberg & Choate, 2005; Rapee, Kennedy, Ingram, Edwards & Sweeney, 2005), and 3) earlier interventions may be more effective than later interventions, possibly due to greater behavioral and neurodevelopmental plasticity in early childhood (Barrett, Lock & Farrell, 2005; Hirshfeld-Becker & Biederman, 2002). Although this chapter focuses on the preschool period, behavior relevant to psychopathology may be identified as early in childhood as possible (Egger & Emde, 2011); for example, endogenous self-regulation typically begins in infancy. Therefore, improving children's emotional and behavioral functioning early in life is essential to enhance children's healthy development (Sroufe, 1979).

Although remarkable advances in preschool psychopathology have increased awareness of emotional and behavioral problems in young children, this work has also highlighted the need for developmentally specific approaches to elucidate the developmental phenotype of preschool psychopathology and promote discovery of mutable mechanisms that can be targeted in early phases of the clinical pathway. Future research should be geared toward advancing a multilevel, developmentally oriented conceptualization of psychopathology that (1) consistent with the RDoC approach, links domains of functioning to various units of analysis such as genetics, neural circuitry, physiologic responses, and observable behaviors (Cuthbert & Insel, 2013; Franklin et al., 2015; Insel et al., 2010; Sanislow et al., 2010); (2) improves empirically based distinctions between typical and atypical behavior across the life span; and (3) uses a multidimensional approach to identify individual profiles of behavior across contexts, informants, and development to shape prevention and treatment efforts. These efforts would be most productively pursued as prospective longitudinal studies with community samples of young children to follow the development, correlates, and outcomes of impairing behavioral profiles.

We argue that the domains proposed in this chapter provide a guiding framework for pursuing developmentally oriented research on early-emerging psychopathology to better characterize normative expression and variability of behavior and risk for psychopathology. Such an approach spans diagnostic categories and minimizes limitations associated with applying diagnostic criteria that impose cut points to phenomena that are dimensional in nature. Although the domains proposed will require revision as researchers further characterize the spectrum of behavior relevant to psychopathology, we view the use of this framework as an essential next step in improving the developmental sensitivity of preschool psychopathology research and its differentiation from normative variation in this age period.

Developmentally sensitive, dimensional, multilevel conceptualizations of psychopathology that are linked to behavior, physiology, and neural circuitry are essential for delineating the normal–abnormal spectrum both in early childhood and across the life span. Although current methods to detect psychopathology are sensitive to and likely appropriate for children demonstrating more severe forms of behavior, the majority of children's behavior is decidedly ambiguous or variable in severity (i.e., existing in a gray area). Therefore, better methods to identify endogenous and exogenous factors that influence children's transitions into and out of normal/typically developing and abnormal/impaired behavior are needed to better understand clinical risk. Further, such factors are complex and transactional in nature; for example, a child who has difficulty with emotion and behavior regulation may be less vulnerable if surrounded by particularly supportive, flexible caregivers and teachers compared to a child with similar difficulties in a more harsh, punitive environment. In addition, interactions among domains are likely to influence conceptualization of a child's behavior. For example, a child with poor self-control but high internalization of rules and standards would likely be less at risk than a child with difficulties across both domains.

Using the domain framework we propose, a profile of children's behavior across the domains would be created that, in conjunction with cross-informant and contextual information about their behavior, temperament, caregiving environment, and culture, would illustrate their clinical risk. The use of individual profiles can shape new intervention efforts to improve behavior and impairment associated with functioning in each domain; for example, treatment could increase flexibility, delay of gratification, and empathy in a child with difficulty in emotion regulation, self-control, and social engagement. Therefore, rather than focus on diagnostic criteria, such efforts would aim to restore typical developmental processes to reduce impairment in functioning and improve children's developmental trajectories across domains.

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CHAPTER 6

The Development of Emotion Regulation: Implications for Child Adjustment

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SETTING THE STAGE

In 1995, in the introduction to a special issue devoted to emotions in the journal *Development and Psychopathology*, Cicchetti and colleagues argued that the study of emotions in atypical populations required consideration of the construct emotion regulation (Cicchetti, Ackerman, & Izard, 1995), which refers broadly to processes that allow an individual to manage emotional arousal. Around that same time, volumes edited by Dodge and Garber (1991) and Fox (1994) addressed the significance of emotion regulation (ER) for both normative and problematic development. These germinal works noted that the ability to control one's emotions in an adaptive manner is critical to everyday functioning for both children and adults. These works also made clear that such skills begin to emerge early in postnatal life, and that their development is influenced by a host of biological, behavioral, and contextual factors. Moreover, they described the development of ER as relatively rapid so that by the time a child enters school, he or she should possess a varied repertoire of emotion regulatory skills that will support the successful transition to the school environment, with its social and academic challenges.

Since the publication of these early works on ER, there have been hundreds of empirical papers published examining the relation between ER and a range of developmental outcomes. This body of literature clearly suggests that the construct has become nearly ubiquitous in accounts of social and emotional development (Eisenberg, Eggum, Sallquist, & Edwards, 2010; Eisenberg & Sulik, 2012; Gross & Thompson, 2007) and in our current conceptualizations of the etiology of psychopathology (Werner & Gross, 2010). In addition, considerable research in the fields of both developmental and clinical psychology provides a blueprint for the emergence of ER skills, the factors that support or undermine their development, and the difficulties children face when they lack the ability to regulate emotional arousal. This work includes research that has examined the underlying biological processes (e.g., Brooker

& Buss, 2009; Dennis & Hajcak, 2009), behavioral correlates (e.g., Calkins, Gill, Johnson, & Smith, 1999; Supplee, Skuban, Shaw, & Prout, 2009), and environmental influences (e.g., Morris, Silk, Steinberg, Myers, & Robinson, 2007; Spinrad, Stifter, Donelan-McCall, & Turner, 2004) that affect the display and development of ER. And these works have guided empirical investigations of the various psychological (Hum, Manassis, & Lewis, 2013; Siener & Kerns, 2012); social (Blair et al., 2013; Chang, Shelleby. Cheong, & Shaw, 2012); and academic outcomes (Graziano, Reavis, Keane, & Calkins, 2007; Herndon, Bailey, Shewark, Denham, & Bassett, 2013) that may be a consequence of various developmental patterns of ER. In this chapter, we consider the development of ER and its role in child adaptation broadly construed, with the goals of (1) elucidating some of the complex mechanisms and pathways that are operating in development; (2) citing challenges and controversies that have emerged through the study of ER and adaptation; and (3) advocating for an integrated approach to the study of ER at all levels of child functioning in the next generation of theory and research in this area.

Although there have been a number of different conceptual and empirical approaches to the study of ER, such work is often conducted from within a developmental psychopathology framework (e.g., Cummings, Davies, & Campbell, 2000; Rutter and Sroufe, 2000). This perspective suggests that there are multiple contributors to maladaptive and adaptive outcomes, that these contributors may interact in various ways within different individuals, and that the consequences for development are multiple pathways to disordered behavior and/or multiple variants of an outcome from individual causative factors (Cicchetti, 1984, 1993; Cicchetti & Rogosch, 1996; Sroufe & Rutter, 1984). Conceptualizing the development of psychopathology in this way highlights the need for complex, process-oriented models of development and emphasizes the importance of conducting longitudinal investigations of the factors that may both influence and be influenced by early contextual, familial, or individual differences. Finally, a developmental psychopathology perspective advocates an organizational view of development; multiple factors, or levels of a given factor, are considered in the context of one another, rather than in isolation (Cicchetti & Dawson, 2002).

Implicit in a developmental psychopathology framework is the notion that biological functioning is an important level of analysis for theoretical and empirical work. This level of functioning incorporates genetic, neural, and physiological processes that, from our perspective, operate in a transactional way with behavioral and social processes. In our view, such a perspective is integral to understanding both normative and nonnormative developmental processes. Thus, in this chapter, we highlight work that utilizes multiple behavioral, biological and relational indicators of ER and the outcomes influenced by ER. We organize the chapter in five sections: (1) definitional and theoretical considerations; (2) developmental and contextual issues; (3) empirical approaches and challenges; (4) relations to child outcomes (including psychopathology, social competence, and academic achievement); and finally (5) implications and challenges for future research. Our overarching aim is to go beyond a summary of research findings to highlight the many conceptual and empirical issues that ought to be considered in studies examining the relation between ER and child outcomes related to developmental psychopathology.

DEFINITIONAL AND THEORETICAL CONSIDERATIONS

Defining the Construct of ER

Numerous definitions of the construct of ER have been offered from within both the child and adult emotion literatures (Gross & Thompson, 2007). However, there has not been clear agreement among these definitions on what the boundaries of the construct are and how these might translate into measurement. Indeed, a decade ago, in the midst of a burgeoning literature addressing the role of ER in psychological and social functioning, Cole and colleagues published a theoretical piece designed to stimulate discussion of these issues and thus the scientific utility of the construct of ER (Cole, Martin, & Dennis, 2004). They challenged researchers to thoughtfully address the complexities inherent in defining and measuring the construct in a way that would allow for meaningful interpretation of research findings. These challenges were potentially serious risks to the field in terms of its commitment to studying a construct that had such intuitive appeal, but clearly required much greater attention to definitional and empirical issues. It is important to note, though, that Cole and colleagues' challenge was in the spirit of recognizing that a scientifically rigorous approach to ER could yield findings that would elucidate processes that distinguished typical from atypical development (Cole et al., 2004).

In our view, this challenge to our field has been fruitful, resulting in more explicit definitions of ER and empirical approaches that map onto those definitions. Our definition reflects recent theoretical and empirical work in both

developmental (Cole et al., 2004; Fox & Calkins, 2003) and clinical psychology (Keenan, 2000) that highlights the fundamental role played by emotion processes in both child development and child functioning (Eisenberg et al., 2000), and, importantly, that is anchored in the measurement of such processes during emotionally evocative situations (Calkins & Hill, 2007). Consistent with many of our colleagues (Eisenberg, Hofer, & Vaughn, 2007; Gross & Thompson 2007), we view ER processes as those behaviors, skills, and strategies, whether conscious or unconscious, automatic or effortful, that serve to modulate, inhibit, and enhance emotional experiences and expressions (Calkins & Hill, 2007). These ER processes are composed of both a reactive and a control dimension (Fox & Calkins, 2003). And, we, like some of our colleagues (Gross & Thompson, 2007), see a value in examining emotional reactivity as distinct from the efforts to manage it. The ER process is clearly a dynamic one in which reactive and control dimensions alter one another across time and levels. Moreover, in our view, the reactive dimension, as opposed to the control dimension, is present and functional early in neonatal life, as it is strongly influenced by genetic and biological factors (Fox & Calkins, 2003). Finally, we note that the display of emotional reactivity and emotional control are implicated in a range of developmental achievements across the life span, including socioemotional functioning and academic performance, and that these indictors of child functioning are often critical factors in the development of behavior problems and various forms of psychopathology (Calkins & Dedmon, 2000; Eisenberg et al., 2007; Thompson & Meyer, 2007).

Two challenges have repeatedly emerged in the translation of definitions of ER to the interpretation of empirical investigations of the construct. First, there has been a tendency to characterize ER as *adaptive* versus *maladaptive* (often using the term dysregulation to capture this quality (Beauchaine, Gatzke-Kopp & Mead, 2007)). And, relatedly, there has been a tendency to view negative affect expression as maladaptive and positive affect expression as adaptive. However, it is important to acknowledge that, conceptually at least, different patterns of emotion expression and regulation may be differentially adaptive based on the goals of the individual and the circumstances in which they are trying to regulate affect (Cole et al., 2004; Thompson & Calkins, 1996). Thus, although it may be challenging to avoid characterizations of particular patterns of ER as more or less adaptive, in the absence of evidence that specific behaviors cause particular problematic outcomes, as opposed to characterize problematic outcomes, it may be prudent to do so.

A second challenge to conceptualizations of ER is how to characterize the integrated nature of seemingly discrete emotional processes. Thus, although many researchers agree that the process of reacting to an emotional stimulus is distinct from efforts to regulate that response, and most measurement strategies reflect this view (cf., Morris, Silk, Steinberg, Terranova, & Kithakye, 2010), the distinction becomes artificial unless one acknowledges that the two processes are often difficult to disentangle and that they interact dynamically across time. Static measurement of either is bound to obscure individual differences in such things as initial level of reactivity, success or failure of particular strategies over time, and whether reactivity constrains regulation or vice versa. In fact, few studies have attempted to either measure cross-time patterns of both processes (Buss & Goldsmith, 1998) or discern patterns of time-linked responding across children.

The dynamic nature of emotional responding leads to the possibility that there are several different dimensions of responding that may be relevant to specific psychological disorders and outcomes. So, it is possible that the relevant aspect of emotion regulation we should be interested in when trying to understand developmental psychopathology will vary depending on the particular features of the outcome of interest. Appraisal may be a process that is more relevant to anxiety disorders (Carthy, Horesh, Apter, & Gross, 2010), for example, so understanding the way appraisal leads to differential patterns of emotional responding, which subsequently leads to increases versus decreases in anxiety symptomatology, may result in a different assessment strategy other than that which is used to examine the relevant emotional processes inherent in externalizing disorders. Framing the issue in this way moves us away from focusing on broad conceptualizations of psychopathology that focus simply on the regulation of anger or fear for example, to a more process-oriented approach that asks questions about the specific dynamics of emotional responding and their relation to behavioral patterns that underlie functioning.

The definition we provide for ER, that it consists of both reactive and control dimensions, and that these dimensions influence behavioral and physiological responding in social and nonsocial contexts, suggests that there are likely to be different theoretical perspectives on how these processes influence the development of psychopathology. Next, we address the dominant perspectives, those that focus on the biological and behavioral characteristics individuals bring to the process of ER, the interpersonal nature of the process, and the implications of these processes for psychological functioning and mental health.

Theoretical Perspectives on ER

Current research and theory in the area of ER and developmental psychopathology has its roots in disparate literatures, including work that focuses on child temperament (e.g., Rothbart & Bates, 1998), parenting and attachment in early development (e.g., Sroufe, 1996), child behavior problems (e.g., Keenan & Shaw, 2003), and biological processes in emotion and cognition (e.g., Lewis et al., 2008; Lewis, Todd, & Honsberger, 2007). Here, we discuss the dominant conceptual approaches within these literatures that have informed current conceptualizations and empirical investigations of ER.

Temperament literature was among the first to specify regulation as a core aspect of the developmental process. The construct of temperament is commonly viewed as the basic organization of personality that is observable as early as infancy and that becomes elaborated over the course of development as the individual's skills, abilities, cognitions, and motivations become more sophisticated (Rothbart & Bates, 1998; Shiner & Caspi, 2003). Temperament thus refers primarily to relatively stable early differences in emotional and behavioral characteristics that have genetic and biological components (DiLalla & Jones, 2000; Goldsmith, Lemery, Aksan, & Buss, 2000). Rothbart and colleagues (Derryberry & Rothbart, 1997; Rothbart, 1981, 2011; Rothbart & Bates, 1998; Rothbart & Derryberry, 1981) have articulated one of the most influential theories of early temperament and one that has generated a great deal of research on infant development over the last twenty years (Buss & Goldsmith, 1998; Calkins, Dedmon, Gill, Lomax & Johnson, 2002: Calkins & Fox, 1992; Stifter & Braungart, 1995). The theory defines temperament along two broad dimensions of *reactivity* and *self-regulation*, which then subsume six subscales that place an emphasis on basic emotion, attention, and motor processes.

With respect to the reactive dimension of temperament, Rothbart notes that the initial responses of an infant may be characterized by their physiological and behavioral reactions to sensory stimuli of different qualities and intensities. This reactivity is believed to be present and observable at birth and reflects a relatively stable characteristic of the infant (Rothbart, Derryberry & Hershey, 2000). Moreover, infants will differ initially in their threshold to respond to visual or auditory stimuli, as well as in their level of reactivity to stimuli designed to elicit negative affect (e.g. Calkins, Fox & Marshall, 1996). The second dimension proposed by Rothbart, that of self-regulation, has been described largely in terms of attentional and motoric control mechanisms that emerge across early development. For example, the development of attention and its use in the control of emotional reactivity begins to emerge in the first year of life and continues throughout the preschool and school years (Posner & Rothbart, 2000; Rothbart, 1989; Rothbart & Bates, 1998). Individual differences in the ability to voluntarily sustain focus or shift attention are paramount to the self-control of attention. Attentional orienting skills, in particular, have been identified as a critical component of the regulatory process, as orienting has the direct effect of amplifying, at a neural level, the stimuli toward which attention is directed, thus changing the affective experience of the individual (Rothbart, Ahadi & Hershey, 1994). Thus, orienting skills assist in the management of both negative and positive emotions, and consequently to the development of adaptive control of emotion and behavior.

Qualitative shifts in attention skills across the first twelve months of life may be integral to the qualitative shifts in ER that are subsequently observed during childhood (Calkins, 2009). However, there are clear individual differences in the ability to utilize attention to successfully control emotion. Those individual differences are likely a function of early differences in neural processing (Thompson, Lewis, & Calkins, 2008), but the development of these foundational regulatory mechanisms clearly takes place in the context of early interactions with caregivers and others, making it important to consider the role of these interactions on emerging skills. An important theoretical perspective that emerged as a function of this observation is that ER may be inherently a social phenomenon (Campos, Walle, Dahl, & Main, 2011; Sroufe, 1996).

In one of the earliest articulations of this point of view, Sroufe (1996) argued that emotional development is inextricably linked with social development, with the course of emotional development described as the transition from dyadic regulation of affect to self-regulation of affect. He argues that the ability to self-regulate arousal levels is embedded in affective interactions between the infant and caregiver. Positive interactions with caregivers, and caregiver intervention that is effective in reducing distress reactions, provides infants with the experience of arousal escalation and reduction (Sroufe, 1996). Such experiences contribute to the working model of affect-related expectations that will transfer from the immediate caregiving environment to the larger social world of peers and others (Cassidy, 1994). Campos (Campos et al., 2011) has also articulated a theory of ER that emphasizes the relational (versus intrapersonal) aspect of ER. The significance of this perspective lies in the fact that human beings are

embedded in social relationships, thus, the person and the environment are intertwined.

Another way of conceptualizing ER and its role in adaptation has come from the child clinical literature. This work places a particular emphasis on emotion regulation and the way specific manifestations of very early problem behaviors are characterized by poor or maladaptive regulatory skills (Cole, Hall, & Radzioch, 2009; Keenan & Shaw, 2003). From a developmental perspective, success or failure at important developmental tasks, like the acquisition of emotion regulation skills during toddlerhood and preschool, likely plays some role in the trajectory of more serious problem behavior as children enter the peer and school contexts (Hill, Degnan, Calkins, & Keane, 2006; Keane & Calkins, 2004). Moreover, from this standpoint, early childhood behavior problems are considered a risk factor for later antisocial behavior and suggest that the mechanisms responsible for ongoing behavioral difficulties are to be found in the interactions between very early child functioning, particularly with respect to the regulation of arousal, and the contexts in which the development of regulation is occurring: namely family and peer relationships.

Although there are large literatures that offer conceptualizations of ER from differing perspectives examining the separate roles of child characteristics, family processes, and psychological functioning, there is a growing interest in the biological processes implicated in emerging ER abilities, child competencies, and maladjustment in particular. For example, Perlman and Pelphrey (2011) document the changes that occur in frontal brain regions implicated in the control of affect across early and middle childhood. Thompson and colleagues (2008) also describe the integration of the neural and physiological mechanisms that serve as the basis of cognitive and affective processes involved in ER. And, behavior genetics research has clearly stimulated growing appreciation for the role of genetic processes in emerging child psychopathology (cf. Horwitz & Neiderhiser, 2011).

Biological processes involved in the regulation of attachment and emotion processes during infancy and early childhood have also been investigated. For example, Hofer (1994; Polan & Hofer, 1999) addressed the multiple psychobiological roles that the caregiver plays in regulating infant behavior and physiology early in life. Based on his research with infant rat pups, he describes these hidden regulators as operating at multiple sensory levels (olfactory, tactile, and oral, for example) and influencing multiple levels of behavioral and physiological functioning in the infant. Moreover, removal of these regulators, during separation, for example, disrupts the infant's functioning at multiple levels. Clearly, then, opportunities for individual differences in the development of emotional self-regulation may emerge from differential rearing conditions providing more or less psychobiological regulation. Thus, perspectives that emphasize the inherently social nature of ER often address both biological and behavioral processes that are both influenced by and influence caregiver–child interactions.

This appreciation of biological processes in child functioning has already led many developmental scientists to reconfigure their models of development to incorporate both genetic and other biological processes as factors in the emergence of complex behavior (Sameroff, 2010; Shonkoff, 2010). And, it is this perspective that has had a major influence on subsequent empirical investigations of ER processes that have adopted the tenets of developmental psychopathology (Beauchaine, Hinshaw, & Gatze-Kopp, 2008; Propper et al., 2008). The conceptual integration of genetics and biology into developmental theories has led to greater appreciation of the complex role of biological processes in transactional models of development that seek to account for the emergence of patterns of adjustment and maladjustment across multiple levels of child functioning. A biopsychosocial perspective motivates *multilevel* research that incorporates biological and behavioral indicators of the factors that may be implicated in complex developmental pathways to outcomes such as child psychopathology. From our view, a broader conceptual framework that incorporates biological, behavioral, and social levels of analyses is essential to better understand the role of ER in the emergence of complex behavioral patterns leading to adjustment and maladjustment. A biopsychosocial perspective is therefore emphasized throughout our review of ER research.

As our review of theoretical perspectives implies, important developmental changes occur in ER processes over the course of development and in the context of important relationships. This developmental process, when viewed from a developmental psychopathology perspective, provides multiple opportunities for continuity and change in the pathways from ER to child outcomes. Next, we provide a brief overview of these developments and address the contexts in which they occur.

DEVELOPMENTAL AND CONTEXTUAL ISSUES

Although some children appear to be quite proficient in the use of basic ER skills at a relatively early age, it is clear

that dramatic growth occurs in the acquisition and display of ER skills and abilities across early childhood (Blandon, Calkins, Keane & O'Brien, 2008). The process may be described broadly as one in which the relatively passive and reactive neonate becomes a child capable of self-initiated behaviors that serve an emotion regulatory function. The infant moves from near complete reliance on caregivers for regulation (e.g., via physical soothing provided when the infant is held) to independent ER (e.g., choosing to find another toy to play with, rather than throwing a tantrum, when the desired toy is taken by a companion), although the variability in such regulation across children, in terms of both style and the efficacy, is considerable (Buss & Goldsmith, 1998; Calkins, in press). As the infant makes this transition to greater independence, the caregiver's use of specific strategies and behaviors within dyadic interactions become integrated into the infant's repertoire of ER skills, across, we presume, both biological and behavioral levels of functioning (Calkins & Dedmon, 2000; Calkins & Hill, 2007). The child may then draw upon this repertoire in a variety of contexts, in both conscious, effortful ways (e.g., walking away from a confrontation with a peer), and in nonconscious, automatic ways (e.g., reducing vagal regulation of the heart to facilitate behavior coping) (Calkins, 2009). Here we address the specific kinds of changes we observe from infancy to adolescence, as well as the dominant contextual influences (parents and peers) that may affect the emergence and use of ER strategies in social and nonsocial contexts.

The Development of ER

Kopp's (1982) seminal treatise on regulation in infancy provided an excellent overview of the early developments in emotional self-regulation. This description has been verified by studies of both normative development (Buss & Goldsmith, 1998; Rothbart, Ziaie, & O'Boyle, 1992) and studies of individual differences (Stifter & Braungart, 1995). These descriptions provide an explanation of how infants develop and utilize a rich behavioral repertoire of strategies in the service of reducing, inhibiting, amplifying, and balancing different affective responses. It is also clear from these descriptions that functioning in a variety of nonemotional domains, including motor, language, cognition, and social development, is implicated in these changes (Kopp, 1989, 1992).

Early efforts at ER, those occurring prior to about three months of age, are controlled largely by physiological mechanisms that are innate (Kopp, 1982). By three months of age, primitive mechanisms of self-soothing, such as sucking, simple motor movements such as turning away, and reflexive signaling in response to discomfort, often in the form of crying, are the primary processes operating, independent of caregiver intervention (Kopp, 1982; Rothbart et al., 1992). The period between 3 and 6 months of age marks a major transition in infant development. First, sleep–wake cycles and eating and elimination processes have become more predictable, signaling an important biological transition. Second, the ability of the infant to voluntarily control arousal levels begins to emerge. This control depends largely on attentional control mechanisms and simple motor skills (Rothbart, Ellis & Posner, this volume; Rothbart et al., 1992; Ruff & Rothbart, 1996), and leads to coordinated use of attention engagement and disengagement, particularly in contexts that evoke negative affect.

By the end of first year of life, infants become much more active and purposeful in their attempts to control affective arousal (Kopp, 1982). First, they begin to employ organized sequences of motor behavior that enable them to reach, retreat, redirect, and self-sooth in a flexible manner that suggests they are responsive to environmental cues. Second, their signaling and redirection become explicitly social as they recognize that caregivers and others may behave in a way that will assist them in the regulation of affective states (Rothbart et al., 1992). During the second year of life, the transition from passive to active methods of emotional self-regulation is complete (Rothbart et al.). Although infants are not entirely capable of controlling their own affect by this age, they are capable of using specific strategies to attempt to manage different affective states, albeit sometimes unsuccessfully (Calkins & Dedmon, 2000; Calkins et al., 1999). Moreover, during this period, infants begin to respond to caregiver directives and, as a consequence of this responsivity, compliance and behavioral self-control begin to emerge (Kopp, 1989). This shift is supported by developments in the motor domain, as well as changes in representational ability and the development of language skills. Brain maturation contributes as well, and by the end of toddlerhood, children have executive control abilities that allow control of arousal, regulation of affective expression, and inhibition and activation of behavior (Bronson, 2000).

Verbal abilities begin to develop in mid to late infancy and as the child moves into the preschool period they contribute to children's ability to regulate and deal with emotional content. As such, the development of language is considered a major milestone in the development of ER (Campos, Frankel, & Camras, 2004). Greater internal state language that develops through parent–child

disclosure of emotion is thought to scaffold children's ability to reflect on their own emotional experience and foster self-awareness, thus resulting in enhanced emotion regulation (Saarni, 1999; Shields et al., 2001). In contrast, language delays that make the use and production of verbal information more difficult may hinder children's ability to successfully utilize effective verbal regulation strategies common during this developmental time period. Children's self-verbalizations of their thoughts and actions have also been suggested as a means through which children may regulate their behavior (Cole, Armstrong, & Pemberton, 2010; Vygotsky, 1962). Taken together, this work suggests that the development of expressive language during preschool allows children to better communicate their needs in socially appropriate ways and enhances their ability understand their own and other's emotional states, therefore facilitating the development of additional tools that aid in the regulation of emotional arousal (Cole et al., 2010).

Across preschool, regulation strategies become more flexible over time to meet contextual demands, allowing children to inhibit or activate behavior accordingly through context-appropriate arousal, planning, and accurate processing of social information in the environment (Eisenberg et al., 2007; Thompson et al., 2008). In an assessment of the trajectories of ER and negativity from ages 4 to 7, ER increased over time (Blandon et al, 2008). There was, however, significant variability in these trajectories indicating that changes in ER over time are susceptible to both individual child factors and also external, environmental factors. As children continue to develop regulatory abilities via modeling, language acquisition, and social interactions, regulation increases while reactivity decreases, though these trajectories are affected, at least to some degree, by early levels of physiological regulation (Blandon et al., 2008).

The practice of these newly emerging skills during the preschool period leads to greater automaticity so that by the time the child is ready to enter the arena of formal schooling, greater effort may be directed toward more demanding academic and social challenges. Importantly, these expanding interactional contexts will place demands that call on the child to integrate emotional and cognitive skills in the service of achieving diverse academic and social goals. Rapid changes have been documented in children's ER and reactivity across early and middle childhood as the capacity for self-regulation increases (Calkins et al., 1999; Calkins & Johnson, 1998; Kochanska, 1994; Kopp, 1989). School-age children are capable of more active and planful regulation strategies including increasing abilities to distract themselves and to reevaluate frustrating and disappointing situations in a more positive manner (Kalpidou, Power, Cherry, & Gottfried, 2004; Stansbury & Sigman, 2000).

Although ER is considered relatively stable from early childhood on (e.g. Raffaelli, Crocket, & Shen, 2005), biological and behavioral aspects of ER continue to be refined into late childhood and early adolescence and are subject to the influence of the environment. Recent evidence from developmental neuroscience suggests that the regions of the brain associated with the ER process include the prefrontal cortex, anterior cingulate cortex, and the amygdala (Beauregard, Levesque, & Paquette, 2004). Brain growth, interconnections in nerve cells, and pruning of connections within these regions occur throughout late childhood and adolescence and are implicated in several domains of functioning including executive functioning, goal directed behaviors, and the regulation of arousal (Giedd, 2008; Spear, 2000).

Late childhood into adolescence is noted as a time of transition, both biologically and environmentally. These transitions are influenced by, and also impact, individuals' experience and expression of emotion. As children enter late childhood, there is a shift in children's developmental contexts, with an increasing emphasis on the peer group and peer influences (Steinberg, 2008). These environmental systems adapt to, and organize themselves around, emerging biological changes within the brain, in hormone levels, and in physical growth. The reciprocal relations that evolve from the interplay between adolescents' social environments and biological changes are believed to have long term impacts on developmental outcomes (Granic, Hollenstein, Dishion & Patterson, 2003).

There is also an emerging literature on the behavioral nature of ER into later childhood and adolescence (e.g. Morris et al., 2007, Raffaelli et al., 2005). With age, children are able to distinguish between both long- and short-term strategies to regulate as they are better able to identify long-term consequences and outcomes of their behavior (Moilanen, 2007). Similarly, children can identify more goals, specifically social goals, for regulating their behaviors. For example, older children expect that displays of negative emotionality are damaging to peer relationships, particularly when the goal is to take care of another's feelings (Shipman, Zeman, & Stegall, 2001; Zeman & Shipman, 1998). Thus, children engage in more sophisticated regulation strategies to mask these negative emotions in front of peers including verbal and facial strategies (Shipman et al., 2001; Zeman & Shipman, 1998). Emotional arousal is heightened during adolescence, likely

due to the fact that neither regulation nor the systems of risk and reward are fully mature. This offset provides links to observed sensation seeking, reckless behaviors, and increased risk for emotional problems (Steinberg, 2004). Further, the increase and instability in hormone levels during adolescence may be implicated in the more labile and negative emotional experiences during this time (Rosenblum & Lewis, 2003).

Research aimed at better understanding the development of emotion regulation again supports the notion that regulatory processes, although grounded in early biological influences like reactivity, are subject to environmental influences and the impact of maturation, and are the means through which these early processes impact later development. Relationships have been described as the inputs and outputs of ER (Bell & Calkins, 2000), therefore highlighting that ER is not only influenced by social partners, but plays a pivotal role in the initiation and maintenance of successful social relationships. As children's social interactions become increasingly more complex, new and unique demands are placed on regulatory processes. Next, we turn to the relationships that likely have the most influence on the development of ER: caregivers and peers.

The Context of ER: Caregiving Practices

One important assumption of much of the research on the acquisition of ER is that parental caregiving practices may support or undermine development and thus contribute to observed individual differences among young children's emotional skills (Morris et al., 2007; Thompson, 1994). As children shift from the more dyadic regulation of infancy to more independent self-regulatory abilities, interactions with parents in emotion-laden contexts teach children that the use of particular strategies may be more useful for the reduction of emotional arousal than other strategies (Sroufe, 1996). Importantly, such interactions both contribute to normative developments and individual variability in ER (Cassidy, 1994).

Although multiple dimensions of caregiving may contribute to the development of self-regulation (Eisenberg, Cumberland, & Spinrad, 1998; Morris et al, 2007), the attachment relationship that develops between caregivers and infants over the first year of life is of particular importance. Current theorizing about childhood attachment and its role in emotional functioning and behavioral adjustment has its roots in the work of John Bowlby (1969/1982), whose evolutionary theory of attachment emphasized the biological adaptiveness of specific attachment behaviors displayed during the infancy period. Such behaviors permit the infant to initiate and maintain contact with the primary caregiver, which serve a survival purpose (Bowlby, 1988). In typical development, infants exhibit a repertoire of behaviors, including looking, crying, and clinging that allow them to signal, and elicit support from, the primary caregiver in times of external threat. Bowlby argued that, by the end of the first year of life, the interactive history between the infant and caregiver, including during times of stress or external threat, would produce an attachment relationship that would provide a sense of security for the infant and significantly influence the child's subsequent adaptation to a variety of challenges (Bowlby, 1988). Emotion regulation theories, specifically, posit that secure attachment relationships, developed through sensitive and supportive caregiver responses, increase children's expectations regarding their own ability to respond to environmental challenge, in addition to increasing the expectations that caregiver intervention will be both available and successful at reducing arousal should children require assistance (Sroufe, 1996). As a result of increased exploration and confidence in one's own abilities to engage in and navigate through emotionally charged situations, a shift from dyadic to self-regulation occurs, resulting in increased self-regulatory capabilities (Sroufe, 1996; Thompson, 1994).

The pattern of findings linking attachment and specific ER behaviors provides support for the important role of caregivers in this process. For example, Diener and colleagues (Diener, Manglesdorf, McHale & Frosch, 2002) observed that attachment classification predicted infants' regulatory strategies during a mildly stressful task in which infants were left with nothing to do while their parent completed a questionnaire. Infants in secure attachment relationships with both parents used strategies emphasizing social orientation. Likewise, in a challenging problem solving task during which the mother was present, toddlers who were classified as secure a year earlier engaged in more maternal help seeking than did avoidant and disorganized toddlers (Schieche & Spangler, 2005). In contrast, mother-reported attachment security was unrelated to the use of mother oriented regulation strategies during laboratory tasks designed to elicit fear and frustration, but was linked with more positive and less negative affect suggesting more adaptive ER among secure children (Smith, Calkins & Keane, 2006). Similarly, infants who were classified as secure at 15 months of age were less likely than avoidant infants to be classified as dysregulated on the basis of high negative affect and defiance during a compliance task at 24 months (NICHD ECCRN, 2004).

Importantly, this effect was significant independent of a variety of demographic characteristics, infant temperament, and maternal sensitivity indicating that the link was robust and not merely an artifact of maternal sensitivity.

Few scholars have examined links between attachment security and emotional regulation processes beyond the infancy period. In a study of preschoolers' use of specific anger control strategies during a waiting paradigm, a secure attachment in infancy predicted greater use of attentional distraction that was linked to successful waiting (Gilliom, Shaw, Beck, Schonberg, & Lukon, 2002). Likewise, 7-year-olds who had been classified as securely attached in infancy reported greater expectations that others would help them emotionally and instrumentally during peer provocations (Ziv, Oppenheim, & Sagi-Schwartz, 2004). This supports the view that children with a secure attachment history have positive expectations of others that may contribute to the use of other-oriented regulation strategies beyond infancy.

Studies examining the relations between specific aspects of parenting thought to be linked to attachment and emotional self-regulation are also of interest when examining the context of ER development. These studies are worth noting because they are mostly conducted with toddlers, children for whom there are clear expectations of emerging autonomous emotional control. In one study of mothers and toddlers, for example, we examined the relations between maternal behavior across a variety of different situations and child emotional self-control in frustrating situations (Calkins, Smith, Gill, & Johnson, 1998). Our analyses indicated that maternal negative and controlling behavior (thought to be reflective of intrusive behavior characteristic of insecure attachment relationships) was related to the use of orienting to or manipulating the object of frustration (a barrier box containing an attractive toy) and negatively related to the use of distraction techniques. Likewise, maternal nonresponsiveness and disengagement following toddler distress cues were linked with children's use of ineffective attentional control strategies during a delay of gratification task (Rodriguez et al., 2005). These data are important in light of findings that the ability to control attention and engage in distraction has been related to the experience of less emotional arousal and reactivity (Calkins, 1997; Crockenberg & Leerkes, 2004; Grolnick, Bridges, & Connell, 1996) and to the display of early externalizing (Calkins & Dedmon, 2000; Crockenberg, Leerkes, & Jó, 2008) and internalizing (Crockenberg & Leerkes, 2006) behavior problems. Finally, maternal sensitivity to infant distress cues, but not nondistress cues, at 6 months was linked with less affect dysregulation at age 2 among temperamentally reactive infants (Leerkes, Blankson, & O'Brien, 2009). That sensitivity to distress was a particularly salient predictor of attachment security in the same sample (McElwain & Booth La Force, 2006), suggests that attachment-related processes may account for this effect.

Although caregiving practices are often attributed a role in the development of ER, the specific processes by which these practices affect children's development are often discussed at a global level (Fox & Calkins, 2003). Greater specificity in *how* caregiving affects children requires a consideration of the multiple levels of functioning that are emerging during early development. As previously discussed, research with infant rat pups demonstrates the importance of caregivers in regulating infant behavior and physiology early in life (Hofer, 1994; Polan & Hofer, 1999). Through hidden regulators operating across multiple sensory levels (e.g., olfactory, tactile, and oral), caregivers play a psychobiological role in the development of infants' behavioral and physiological functioning. So, for example, maternal tactile stimulation may have the effect of lowering the infant's heart rate during a stressful situation, which may in turn, support a more adaptive behavioral response. Moreover, removal of these regulators, during separation or distress, for example, is thought to disrupt infants' functioning. Consistent with this view, maternal holding and rocking are particularly effective at reducing infant distress (Jahromi, Putnam, & Stifter, 2004) and mother–infant skin-to-skin contact has been linked with greater physiological and emotional regulation among premature infants (Feldman, Weller, Sirota, & Eidelman, 2002). Findings have also consistently demonstrated that maternal sensitivity is associated with effective autonomic regulation in response to challenge, and, conversely, that negative, controlling behaviors are related to poor autonomic nervous system (ANS) regulation (e.g., Calkins, Graziano, Berdan, Keane, & Degnan, 2008; Calkins et al., 1998; Conradt & Ablow, 2010; Ham & Tronick, 2006; Moore et al., 2009; Propper & Moore, 2006).

Importantly, evidence from animal models also suggests that caregiving affects infants' biological and behavioral systems of regulation through the environment the caregiver provides rather than through shared inherited traits. For example, Meaney and colleagues have shown that high levels of maternal licking/grooming and arched backed nursing in rats affects the neurological systems associated with the stress response, a process that has a long-term influence on stress-related illness, certain cognitive functions, and physiological functions (Caldji et al., 1998; Champagne & Meaney, 2001; Francis, Caldji, Champagne,

Plotsky, & Meany, 1999). Furthermore, cross-fostering studies demonstrate convincingly that these maternal behaviors are transmitted behaviorally through the nursing mother and not through the biological mother, indicating that early caregiving is a crucial factor in early development and may affect the organism's level of emotional reactivity even when they reach adulthood (Calatayud, Coubard, & Belzung, 2004; Champagne & Meaney, 2001).

Longitudinal studies have been more informative about the relations over time between caregiving and physiological regulation in infants. One recent study (Propper et al., 2008), identified children who might be at genetic risk for problems with regulation because they carried the risk allele of the dopamine transmitter gene DRD2. The findings revealed that infants without the risk allele displayed appropriate cardiac vagal regulation in a laboratory paradigm that was challenging to the infants, and this pattern held across the first year. Infants with the risk allele, however, displayed a different pattern of results, depending on the level of caregiver sensitivity to which they were exposed. For infants with the risk allele and mothers who were not sensitive, poor physiological regulation was observed across the first year. Infants with the risk allele and mothers who were sensitive displayed poor physiological regulation during assessments at 3 and 6 months of age, but by the end of the first year, their pattern of physiological responding to challenge was no different than the infants without the risk allele. This G×E interaction demonstrates convincingly that infants and caregivers each bring something to the developmental process of acquiring regulatory skills very early in development.

The Context of ER: Peer Relationships

Peer interactions offer a socialization experience that places different demands on children's regulatory abilities than those of parent–child interactions. Typically, research examines the influence of emotion regulation on interactions with peers. For example, children's anger reactions that are less constructive, such as venting and physical retaliation, have been shown to be related to greater emotional intensity and less socially adaptive behavior, but children who employ more constructive methods are rated as having better social skills and social status as well as lower aggression and emotional intensity (Eisenberg, Fabes, Nyman, Bernzweig, & Pinuelas, 1994). Similarly, maladaptive behaviors with peers have been found to be associated with lower social status, peer-reported social behaviors such as engaging in fighting and bossiness in boys, and ratings of aggressiveness and sneakiness for girls (Keane & Calkins, 2004). Given these findings, it is of no surprise that children who lack the regulatory abilities necessary for successful social interaction also have fewer mutual friendships (Dishion, Piehler, & Myers, 2008). Thus, a body of research indicates that children who are well regulated develop the social skills necessary to form successful peer relationships, and children who display deficits in ER abilities have difficulties engaging in positive social interactions and developing positive relationships with peers.

Although ER has been consistently shown to influence children's social skills and peer interactions, the development of ER abilities are also developed in and facilitated by peer relationships (Howes, 2009). Children who are highly reactive and have difficulty regulating their emotions are viewed by peers as socially unskilled or aggressive and, as a result, they are less likely to engage in positive peer interactions and develop friendships that provide beneficial socialization experiences. Increased participation in social contexts with multiple social partners affords children greater opportunities for the development of more sophisticated ER abilities. Time spent in friendships, for example, allows children to practice interpersonal skills that would not be provided by other kinds of relationships such as the parent–child relationship (Laursen, Finkelstein, & Betts, 2001). Maintenance of friendships offers opportunities to develop conflict resolution skills and note the outcomes of these strategies (Fonzi, Schneider, Tani, & Tomada, 1997). Finally, lasting friendships provide children evidence for the continued reward of adaptive social skills (Laursen et al., 2000).

Although friendships may serve as a developmental resource in the socialization of adaptive regulatory behaviors when the identity and qualities of a friend are positive, friendships with children who engage in maladaptive behaviors may impede the development of ER. Continued participation in deviant behaviors limits the development of social and emotional competencies including ER. In turn, children are more susceptible to peer influence as they lack the planning and impulse control necessary to decline participation in the negative behaviors endorsed by their friends (Dishion et al., 2008). By engaging in these maladaptive behaviors with similarly deviant peers, children are unlikely to develop the competencies necessary to enhance their ER and resist negative influences. Individual differences in self-regulation may serve as a protective factor from deviant peer influence, as a well-regulated adolescent is less susceptible to the immediate rewards posed by engaging in deviant talk or behavior among their peers (Gardner, Dishion, & Connell, 2008). This may be

supported by the finding that deviant youth experience greater susceptibility to peer influence (Brown, Clasen, & Eicher, 1986; Steinberg & Monahan, 2007). Similarly, self-control has been found to moderate the link between deviant peers and delinquent behavior given that a lack of self-control leads to maladaptive behaviors (McGloin & Shermer, 2009). This work suggests that ER is necessary for youth to avoid succumbing to negative peer influence and poor regulation is associated with a vulnerability to engage with deviant peers (Dishion et al., 2008).

Our review of the development of ER and the contextual influences that may be observed during development suggests that caregivers and peers can serve to facilitate the acquisition of ER skills or disrupt the process of developing those skills. Importantly, though, this development is somewhat dynamic and the nature and degree of contextual influence may vary as a function of both where the child is developmentally and in terms of their general level of psychological functioning. The challenge of modeling these pathways over time is significant. Moreover, as we see in the next section, measuring and quantifying the ER processes themselves poses significant challenges that are also in part a function of studying development in context.

EMPIRICAL APPROACHES AND CHALLENGES

Early emotion regulation research focused on single method measurement approaches and on assessments of constructs thought to reflect ER or ER deficits (such as behavior problems) rather than on the measurement of the construct itself. A conceptualization of ER that acknowledges the biological, psychological, and social components of the construct implies a multimethod approach to studying ER and its relation to child functioning. Thus, in the following section we first discuss methodological considerations related to measuring ER and then highlight approaches in which behavioral, biological, and social processes integral to the regulation of emotion are assessed. In addition, because ER develops through transactional associations at multiple levels in a variety of contexts across development, the consideration of the environmental context and children's developmental status are also considered.

Developmental and Contextual Implications for Measurement

One of the most significant challenges to the study of the development of ER and its relation to adaptive versus maladaptive behavior is that the manifestation of ER abilities changes significantly over time. Because of its dependence on the maturation of prefrontal-limbic connections, the development of emotion regulatory skills is relatively protracted (Beauregard et al., 2004), and extends from the emergence of basic and automatic regulation of biological processes in infancy to the more self-conscious and intentional regulation of behavior and cognition in middle childhood and adolescence (Ochsner & Gross, 2004). Further, development from infancy through adolescence is marked by continuous changes and restructurings within and across many relevant psychological and biological domains, including emotional, social, cognitive, and neural development. To be empirically valid, measures need to be sensitive enough to capture developmental changes associated with these reorganizations and to assess the construct in a developmentally appropriate manner (Zeman, Klimes-Dougan, Cassano, & Adrian, 2007).

For example, infants and young children are not often developmentally capable of articulating their specific emotional experience; thus, observational indicators of emotional expression and regulation may be more informative and age appropriate during infancy and early childhood than during middle childhood or adolescence when regulation abilities become more internalized and display rules influence the behavioral indicators of ER. Further, depending on the age of the child, certain behavioral and physiological responses may be considered more or less adaptive. For example, physical self-soothing behaviors are thought to be an adaptive ER strategy in infancy and toddlerhood (Rothbart, 1989). However, once children move beyond infancy and develop more advanced attentional, verbal, and social skills, self-soothing behaviors are considered to be an immature way to regulate emotion and more sophisticated strategies are expected. Similarly, a strong physiological response to a stranger may be adaptive and developmentally appropriate at 9 months, but the same physiological response in middle childhood may be an indicator of maladjustment. Thus, consideration of the developmental time period during which ER is being assessed is important for the selection, utility, and validity of ER measures.

In addition to considering the developmental time period, the measurement of ER cannot be considered outside of the environmental context in which the emotion is embedded (Campos et al., 2011). ER is often defined as the ability to modulate emotional expressions and experiences in a way that allows for the accomplishment of one's goals (Calkins, 2004b; Thompson, 1994), and goals vary based on specific social situations. Therefore,

the adaptive nature of the physiological and behavioral processes underlying emotional control is often dependent on the context in which the emotion is experienced or expressed. For example, physiological responses that are thought to underlie the generation of coping behaviors may be adaptive within a threatening environmental context. However, the same physiological response may be considered maladaptive within a context of social engagement or cognitive challenge. And indeed, although many studies have found greater vagal withdrawal to be associated with adaptive developmental outcomes, empirical work assessing the functional role of cardiac vagal functioning in the development of psychosocial adjustment has shown moderate vagal withdrawal or augmented vagal reactivity to be related to optimal functioning in some cognitive and social contexts (Hastings et al., 2008; Marcovitch et al., 2010). Relatedly, if we consider a child engaged in a frustration task, employing caregiver oriented strategies may only be adaptive if the caregiver is readily available to intervene or serve as a distraction, and problem focused strategies may only be useful at reducing arousal if the frustrating situation has the potential to be manipulated by the child. Therefore, although there is a variety of measures utilized in the assessment of ER, the assumptions made about the adaptive nature of behavioral and physiological emotional responses should be considered in conjunction with the environmental context in which the emotion is elicited.

Approaches to Assessing ER

Behaviors and Strategies

Emotions are thought to initiate and guide behavior such that the experience of negative arousal, such as intense anger or fear, prompts individuals to engage in behaviors that will lessen the intensity of the negative emotion experienced (Youngstrom & Izard, 2008). Researchers studying the regulation of emotion have defined behaviors that are enacted to modulate or maintain emotional arousal as ER strategies (Thompson, 1994). Although it is necessary to regulate both positive and negative emotion, individual differences in children's abilities to control negative arousal have been found to be particularly salient to the understanding of developmental psychopathology. Thus, the majority of ER research has focused on children's abilities to manage emotional distress through the measurement of behavioral strategies used to regulate negative emotion. The development and use of ER strategies can vary across development as the result of increased attentional abilities, memory, and cognitive function. Thus, in addition to discussing commonly measured behavioral strategies, we highlight the salience of each strategy for different developmental time periods.

Observed Strategies of Early Childhood. Because young children have relatively limited physiological, attentional, and cognitive abilities, emotion regulation strategies tend to be more behaviorally based and are therefore more easily observed during the infancy, toddler, and preschool periods than later in development. To observe children's ER strategies, researchers often devise experimental paradigms to elicit a variety of negative emotions by simulating situations children experience on a daily basis (Goldsmith, Reilly, Lemery, Longley, & Prescott, 1999; Goldsmith & Rothbart, 1993). Examples of such simulations include frustration paradigms, in which children are blocked from a desired goal (e.g., Dollar & Stifter, 2012), fear paradigms, in which children engage with an unpredictable or frightening object (e.g., Hane, Fox, Henderson, & Marshall, 2008), disappointment paradigms (e.g., Durbin, 2010), in which children receive an undesirable gift when they were expecting a more exciting one, and delay of gratification paradigms (e.g., Kochanska & Knaack, 2003) in which children are asked to withhold their engagement with a desirable object. In addition to variation in the type of emotion-eliciting task, paradigms differ with regard to who is present. Some tasks are designed to observe mother–child interactions during common negatively charged situations, such as the discussion of conflict (e.g., Allen, Hauser, Bell, O'Connor, 1994), or the clean up of toys (e.g., Kochanska, Coy, & Murray, 2001). Other tasks require children to comply with an experimenter (Goldsmith & Reilly, 1993), or engage with a peer or a social setting (e.g., Lam, Dickerson, Zoccola, & Zaldivar, 2009), and some tasks are performed completely independently (Goldsmith & Rothbart, 1993). Strategies to regulate emotions may vary, or be more or less adaptive, depending on the type of task, who is involved and available, and the age of the child (Grolnick, McMenamy, Kurowski, 2006; Zeman et al., 2007). For this reason, when examining the associations between ER strategies and child adjustment, consideration should be given to the type of emotional challenge and the available social partners.

ER strategies observed within these paradigms have been organized within behavioral ER categories including self-soothing or self-comforting, orientation toward a caregiver, disengagement of attention, avoidance, and approach (Gross, 1998; Rothbart & Derryberry, 1981; Rothbart et al., 1992). These observed regulatory strategies are most commonly measured in terms of presence, frequency, or duration. For example, researchers can

observe and record whether or not a child engaged in specific regulatory behaviors, the number of times a child employs a particular regulatory strategy, or they may document the length of time the child engages in different strategies (Dollar & Stifter, 2012; Graziano, Calkins, & Keane, 2010; Mirabile, Scaramella, Sohr-Preson, & Robinson, 2009; Perry, Calkins, Nelson, Leerkes, & Marcovitch, 2012; Trentacosta & Shaw, 2009). Below, we highlight commonly observed regulatory strategies measured during experimental contexts designed to elicit negative emotional arousal.

Self-Soothing Physical self-soothing behaviors include sucking on the fingers or gums, engaging in repetitive or gentle rubbing, hair twirling, or hand clasping (Diener & Mangelsdorf, 1999; Rothbart, 1989). Although physical self-soothing is a primary regulatory strategy observed in early infancy, children's increased attentional control and locomotive capabilities often forecast a normative decrease in physical self-soothing and an increase in more sophisticated behaviors by age 2 (Grolnick et al., 1996; Mangelsdorf, Shapiro, & Marzof, 1995; Rothbart, 1989). As children's language and representational capabilities develop, use of symbolic self-soothing often emerges. Specifically, children may regulate and comfort themselves by mentally transforming a distressing emotional situation into a manageable one by developing game-like activities around the source of distress (Grolnick et al., 2006).

Orientation Toward a Caregiver Although there is a shift toward more autonomous self-regulation of emotion, ER is not always independent from others or accomplished alone; children can utilize caregivers in a way that assists in the regulation of emotion without being dependent (Grolnick et al., 2006). For example, a child who initiates a conversation with a caregiver during a stressful situation is quite different from a child relying on a mother to intervene and take responsibility for reducing his or her arousal. Thus, caregiver-oriented behaviors that children employ such as social referencing, proximity seeking, help seeking, and bids for attention are often used as indictors of child-initiated attempts to reduce arousal by facilitating coregulation between themselves and their caregiver (Diener et al., 2002; Perry et al., 2012; Supplee et al., 2009).

Disengagement of Attention Infants are able to voluntarily shift their attention between 3 and 6 months of age (Rothbart, Posner, & Boylan, 1990), and a number of empirical studies have shown that infants who are able to disengage and avert their gaze from emotional arousing stimuli show decreased negative affect (e.g., Buss & Goldsmith, 1998; Crockenberg & Leerkes, 2004; Stifter & Braungart, 1995). As attentional networks mature and children develop increased autonomy, they begin to more actively re-direct attention through the use of distraction strategies. Thus, attentional distraction behaviors characterized by shifting attention to less emotionally relevant aspects of a situation, or away from the situation entirely, are commonly observed in early childhood and can serve to reduce emotional arousal (Grolnick et al., 2006; Gross, 1999).

Avoidance Avoidant regulatory behaviors include moving or turning away from the negative stimuli or leaving the emotionally charged context (Gross, 1999). Increased autonomy in movement allows children to decrease negative arousal by physically and mentally disengaging from the source of arousal. For example, avoidant strategies observed in early childhood may include movement away from negative stimuli or attempting to leave a negative situation.

Approach Approach strategies involve maintaining or increasing attentional focus and engagement with the source of arousal and are utilized as a means of regulation throughout childhood (e.g., Compas, Connor-Smith, Saltzman, Thomsen & Wadsworth, 2001; Grolnick et al., 1996). Observed problem solving responses such as brainstorming solutions to a problem, or planning a course of action, are specific and conscious attempts to modulate arousal by changing a distressing situation and attempting to control the consequences that may arise as a result of a negative event (Aldao & Nolen-Hoeksema, 2010; Aldao, Nolen-Hoeksema, & Schweizer, 2010). It is important to note that although attention and problem-focused engagement with the source of negative arousal may be effective at reducing distress in some instances, attempting to alter an environment that cannot be changed (i.e., continued searching for the mother during separation) may in contrast heighten negative arousal (Grolnick et al., 1996).

Cognitively Based Strategies of Middle Childhood and Adolescence. As children develop increased attentional abilities, memory, and cognitive function, strategies used to regulate emotion are thought to become more internal and cognitively based (Kopp, 1982). Therefore, researchers are often unable to observe regulatory strategies beyond early childhood and begin to rely more heavily on alternative measurement strategies. Although a number of studies ask children and adolescents to report on the frequency or likelihood of employing specific regulatory strategies (Aldao, Mennin, McLaughlin, 2013; Gullone et al., 2010; Hsieh & Stright, 2012; Martini & Busseri, 2012; Romens & Pollak, 2012), many researchers design experimental paradigms in

which they teach or instruct children to use different strategies to modulate negative arousal (Carthy, Horesh, Apter, Edge, & Gross, 2010; Davis & Levine, 2013; DeCicco, Solomon, & Dennis, 2012; Dennis & Hajcak, 2009; McRae et al. 2012); by controlling which type of strategies children employ and comparing strategy use to the experience of negative emotion, researchers are able to better understand the regulatory function and developmental implications of each regulatory behavior. Below we highlight three commonly measured ER strategies throughout middle and late childhood: cognitive reappraisal, rumination, and suppression.

Cognitive Reappraisal Cognitive reappraisal refers to altering the way an individual thinks about a situation to change its emotional impact (Werner & Gross, 2009). In an effort to reduce arousal, individuals may attempt to change the situation's emotional significance by generating neutral or positive interpretations of emotionally charged contexts, or change their belief in the extent to which they can control the situation (Aldo et al., 2010; Gross, 1998, 1999). For example, if a child was anxious over an exam, they may remind themselves that it is only a test and acknowledge their ability to manage the demands of the exam through studying and preparation.

Rumination Rumination involves repetitive attentional focus on thoughts and feelings surrounding negative emotional contexts. Although individuals often engage in rumination as a way of decreasing negative arousal around a specific emotion-eliciting situation (Papageorgiou & Wells, 2003), rumination increases attention to the source of negative arousal and thus may produce more intense and longer lasting experiences of negative emotion (Gross, 1999).

Suppression Another avoidant strategy used in late childhood and adolescence is expressive suppression of negative emotion. An example of this may be a child maintaining a neutral face while children on the playground are teasing her. Although suppression of negative emotion may reduce negative arousal and the subjective experience of negative emotion temporarily, it may be less effective at reducing arousal over an extended period of time (Gross, 1998).

Reported Measures of ER

To gain additional insight into children's ability to emotionally regulate with different social partners within and across different environmental contexts, parent report, teacher report, and self-report measures are often utilized. Although it is important for researchers to consider the challenges associated with reported measures of ER, such as whether children are developmentally capable to accurately reflect and report on their own emotional competence, whether parents and teachers are objective, and whether there is concordance across reporters (Zeman et al., 2007), reported measures of children's ER have several advantages. First, social contexts in which emotions take place can have a large impact on the emotion experienced, the extent to which the emotion is expressed, and the specific strategies or skills used to modulate that emotion. Therefore, both other and self-report measures provide an index of children's regulatory capabilities across a wide variety of settings outside the laboratory that might not have otherwise been obtained. Second, observed measures don't reveal insight into the reasoning and motivation behind emotional behavior that children's self-reported measures may uncover (Zeman, et al., 2007). Finally, reported measures of ER are easier to obtain than observed or physiological indices, and the Likert scales often associated with them can allow for greater variability in the report of ER capabilities.

Self-report. Although there has been an increased interest in the construct of ER and its association with the development of psychopathology across the last 20 years, there are a surprisingly small number of validated questionnaire measures within this area, and measures of children's self-reported ER are particularly scarce. Most self-report measures designed to assess ER specifically, including the ER Questionnaire (ERQ; Gross & John, 2002), the Difficulties in ER Scale (DERS; Gratz & Roemer, 2004), and the Cognitive ER Questionnaire (CERQ; Garnefski, Kraaij, & Spinhoven, 2001), have primarily been developed and used with adults. However, a few studies have used these measures in developmental populations (e.g., Garnefski, Boon, & Kraaji, 2003; Gullone, Hughes, King, & Tonge, 2010; Neumann, van Lier, Gratz, & Koot, 2010). Moreover, self-report measures utilized with children often focus on a specific regulatory strategy, emotion, or general emotionality from a temperament perspective. Examples include the Pediatric Anger Expression Scale-III (PAES-III; Jacobs, Phelps, & Rohrs, 1989), which measures anger turned inward, anger expressed outwardly, and anger controlled cognitively or behaviorally, the Early Adolescent Temperament Questionnaire (EATQ-R; Capaldi & Rothbart,1992), which measures self-regulation, reactivity, and emotionality (Cox, Stabb, and Hulgus, 2000; Hewitt et al., 2002), the How I Feel (HIF; Walden, Harris & Catron, 2003), which measures the intensity and control of emotion, and the Children's Worry Management Scale (CWMS;

Zeman, Cassano, Suveg, & Shipman 2010), which assesses children's self-reported methods of regulating worry (i.e., suppression of worry, exaggerated displays of worry, and constructive ways of managing worry). More recently, however, Phillips and Power (2007) have developed the Regulation of Emotions Questionnaire (REQ) to assess the frequency with which adolescents use both functional and dysfunctional ER strategies to regulate emotions.

Other-report. Because infants and young children are often not capable of self-reporting their own ability to manage and control emotional arousal, the majority of other-reported questionnaires are designed for and used with parents of young children. However, many have been successfully implemented with teachers and day care providers (e.g., Fujiki, Spackman, Brinton & Hall, 2004; Goldsmith, Rieser-Danner, & Briggs, 1991; Ramsden & Hubbard, 2002). Similar to self-reported measures of ER, other-report measures specifically assessing children's ability to modulate emotional arousal are limited. Often, scales of the Infant Behavior Questionnaire (Rothbart, 1981), the Toddler Behavior Questionnaire (TBQ; Hagekull, 1985), Child Behavior Questionnaire (CBQ, Rothbart 1981; CBQ-VSF, Putnam & Rothbart, 2006) and the Child Behavior Checklist (CBCL; Achenbach, 1991), which assess negative affectivity, emotional reactivity, and self-regulation, have been utilized within the ER literature (e.g., Batum & Yagmurlu, 2007; Carter, Little, Briggs-Gowan, Kogan, 1999; Goldsmith, Buss, & Lemery, 1997). However, the most frequently used measure given to parents and teachers designed to specifically assess children's ability to modulate emotional arousal is the ER Checklist (ERC; Shields & Cicchetti, 1997), which addresses parents' perceptions of their children's ER and emotionality. Although useful, the ERC provides a more general account of children's ER and does not provide information on regulation of specific types of emotions or strategies used to regulate emotion. Thus, additional parent-reported measures of children's ER strategies are needed.

Biological Measures of ER

In addition to assessing the regulation of emotion through observations and reports, there has been an increase in the use of measures of underlying physiological responses in the expression and experience of emotion. The use of physiological measures is advantageous in that it allows for assessment at a level of child functioning that is often thought of as foundational to the development of subsequent skills (Lewis & Todd, 2007), and identifies underlying mechanisms integral to the regulation of emotion that cannot be observed or communicated through observation alone. Moreover, assessing physiological biomarkers of specific patterns of emotional responding allows for greater insight into the bidirectional associations between behavior and physiology, allowing developmental researchers to identify important aspects of the physiology-behavior connection for developmental trajectories (Fox, Hane, & Pérez-Edgar, 2006). Over the last decade, researchers attempting to better understand the physiological underpinnings of ER have primarily focused on autonomic arousal, activation of the hypothalamus-pituitary-adrenal (HPA) system, frontal electroencephalographic asymmetry underlying the experience and control of emotion, and event-related potentials in response to emotional stimuli. Thus, in the section below we discuss the measurement of activation within each physiological system and its relation to ER and developmental psychopathology.

Autonomic Arousal. ER theories that focus on the underlying physiological components highlight the maturation of the autonomic nervous system (ANS) as playing a fundamental role in the regulation of emotion and behavior (Santucci et al., 2008). The ANS is composed of two branches: the excitatory sympathetic nervous system (SNS) and the inhibitory parasympathetic nervous system (PNS). The primary job of the ANS is to maintain the body's homeostasis; therefore, the two subsystems work in conjunction to increase or decrease physiological arousal in an organ or system. The SNS is primarily dominant during threatening or stressful situations and produces increased physiological arousal (i.e., increased heart rate, dilated pupils) to meet environmental demands, while the PNS is primarily dominant during calm and restful periods to maintain homeostasis. Given the complexity of ANS functioning, ER researchers often investigate PNS and SNS responses and their association to behavior during environmental contexts that are perceived as challenging or threatening. Thus, we discuss the measurement of both sympathetic (i.e., rejection period and electrodermal activity) and parasympathetic (i.e., heart rate variability, or vagal tone) activation, and their relation to emotional behavior and adjustment.

Preejection Period Preejection period (PEP) is defined as the sympathetically mediated time interval between the onset of ventricular depolarization and the onset of left ventricular ejection (i.e., ejection of blood into the aorta; Brenner & Beauchaine, 2011; Brenner, Beauchaine, & Sylvers, 2005; Fox et al., 2006) and is measured by simultaneously collecting both electrocardiogram and

impedance cardiography. PEP can serve as an estimate of sympathetic influences on the heart because it usually reflects changes in how forceful the heart contracts (Stern, Ray, & Quigley, 2001). PEP is negatively correlated with sympathetic activation such that lower values represent increases in sympathetic activity while higher values indicate decreased sympathetic activity. Sympathetic reactivity, as measured by PEP, has been found to be related to toddlers' freezing behaviors during mildly threatening stranger interactions (Buss, Davidson, Kalin, & Goldsmith, 2004), children's memory of stressful events (Quas, Carrick, Alkon, Goldstein, & Boyce, 2006), externalizing behaviors in middle childhood (Boyce et al., 2001), the presence of conduct disorders in adolescence (Beauchaine, Katkin, Strassberg, & Snarr, 2001), and ER (Stifter, Dollar, Cipriano, 2011).

Electrodermal Activity Another way of assessing sympathetic nervous system activation is through the measurement of electrodermal activity (EDA), or skin conductance. EDA results from activity of eccrine sweat glands, a special type of sweat gland concentrated on the palms of the hands and the soles of the feet. Specifically, when environmental stimuli activate the sympathetic nervous system, sweat rises toward the skin's surface and eccrine sweat glands act as resistors. The hydration of the skin associated with the increase in sweat creates greater skin conductance and lower skin resistance. To measure skin resistance, researchers pass a small current between two electrodes on the skin. Thus, the measurement of skin conductance is the extent to which electrical conduction is increased and skin resistance is decreased (Dawson, Schell, & Filion, 2000; Stern et al., 2001). Empirical work has found measures of electrodermal responsivity to be associated with preschoolers' emotional expression (Cole, Zahn-Waxler, Fox, Usher, Welsh, 1996), delinquency symptoms in middle childhood (El-Sheikh, Hinnant, & Erath, 2011), and adolescents' behavioral warmth (Diamond & Cribbet, 2013).

Respiratory Sinus Arrhythmia Pathways of the parasympathetic nervous system serve to modulate changes in sympathetic activity and are therefore thought to play a critical role in the regulation of emotion (Porges, 2003). Specifically, the myelinated vagus nerve, originating in the brainstem nucleus ambiguous, provides input into the sinoatrial node of the heart, producing dynamic changes in cardiac activity that allow the body to transition between sustaining metabolic processes and generating responses to the environment (Porges, 2007). Parasympathetic influences on heart rate can be quantified by measuring heart rate variability that occurs at the frequency of breathing (i.e., respiratory sinus arrhythmia, RSA). Two common ways of measuring RSA include the peak-to-valley method (Fouad, Tarazi, Ferrario, Fighaly, & Alicandri, 1984) and spectral analysis (Porges, 1986). The peak-to-valley method quantifies RSA by a breath-by-breath measure of heart rate that represents the difference between the longest and shortest heart period within the respiratory cycle (Grossman & Svbeak, 1987). Using spectral analysis, Porges (1986) applied an algorithm to detrend periodicities in heart period (HP) slower than RSA. A band-pass filter then extracts the variance of HP within the frequency band of spontaneous respiration. A multitude of empirical studies have linked parasympathetic activity, as measured by RSA, with the regulation of emotion (e.g., Brooker & Buss, 2009; Gentzler, Santucci, Kovacs, & Fox, 2009; Moore, 2009; Vasilev, Crowell, Beauchaine, Mead, & Gatzke-Kopp, 2009) and behavioral outcomes such as internalizing and externalizing problems (e.g., Fortunato, Gatzke-Kopp, Ram, 2013; Graziano & Derefinko, 2013; Hastings et al., 2008; Hinnant & El-Sheikh, 2009).

The Hypothalamic-Pituitary-Adrenocortical System. The most common way of assessing activation of the hypothalamic-pituitary-adrenocortical (HPA) axis is through the measurement of the hormonal product of this system, cortisol. Although most developmental researchers obtain cortisol through noninvasive saliva samples, it can also be assessed in the blood or urine. As part of the body's normal functioning, the hypothalamus produces both a cortisol-releasing hormone (CRH) and vasopressin. In combination, CRH and vasopressin stimulate the anterior pituitary gland to produce adrenocorticotrophic hormone (ACTH). ACTH is then released into general circulation and stimulates cells in the adrenal glands to produce and release cortisol into the bloodstream (Chrousos & Gold, 1992). Although cortisol production varies rhythmically in the course of a 24-hour period, psychological stressors increase cortisol above basal levels at that time of day. Therefore, cortisol reactivity to emotional contexts and stimuli has been of particular interest to ER researchers and has not only been associated with children's regulation of emotion (e.g., de Veld, Riksen-Walraven, & de Weerth, 2012; Lam et al., 2009; Stansbury & Gunnar, 2004; Zimmerman & Stansbury, 2004), but internalizing and externalizing behaviors as well (e.g., Alink et al., 2008; Allwood, Handwerger, Kivlighan, Granger, & Stroud, 2011; Bagner, Sheinkopf, Vohr, & Lester, 2010).

Electroencephalographic Activity.

Frontal Electroencephalographic Asymmetry Researchers have suggested the possibility that the brain systems assessed by frontal e lectroencephalographic (EEG) asymmetries may moderate or mediate emotional experience

and responding (Fox, 1991, 1994; Fox & Davidson, 1987). EEG is collected via electrodes placed on the scalp and electrical activity is recorded and referenced to inactive electrode sites. The electrical signal collected via the electrodes is thought to be derived from the aggregate of postsynaptic potentials and EEG power is summed across frequency bins to form measures of band power (Fox et al., 2006). A number of studies have shown that the association between asymmetry and behavioral activation is specific to anterior brain regions (Sutton & Davidson, 1997). Therefore, the most common ways to measure EEG asymmetry is by subtracting the natural log of left hemisphere alpha power from the natural log of right hemisphere alpha power (ln[right alpha] − ln[left alpha]) at frontal electrode sites. This approach results in a one-dimensional scale representing the relative activity of the right and left hemispheres, with the middle point of the scale equaling zero or symmetrical activity (Coan & Allen, 2004). Because alpha power reflects the inverse of activation, higher scores indicate relatively greater left frontal activity whereas lower scores indicate relatively greater right frontal activity (i.e., a leftward and rightward asymmetry). Within the ER and psychopathology literature, EEG asymmetry has been frequently measured and related to behavioral adjustment and mental health (Curtis & Cicchetti, 2007; Gatze-Kopp, Jetha, & Segalowitz, 2012; He et al., 2010; Santesso, Reker, Schmidt, & Segalowitz, 2006).

Event-Related Potentials In addition to EEG asymmetry, recent work in developmental neuropsychology has begun to examine the relation between event-related potentials (ERPs) and emotion regulation. ERPs are electrical potentials generated by the brain and reflect the synchronous activity of neurons (Luck, 2005). Unlike spontaneous EEG, which is recorded continuously across time, ERPs are time-locked to specific events (i.e., the presentation of a stimulus or the execution of a response), resulting in positive or negative voltage changes over time (Hajcak, MacNamara, & Olvet, 2010). Because the ERP is smaller in voltage than spontaneous EEG, ERPs are commonly assessed by repeatedly presenting a stimulus and averaging the electrocortical signal to each of these stimuli (Stern et al., 2001). Although a relatively small amount of empirical work has assessed the associations between ER and ERPs, interest in this area has been rapidly growing and associations between multiple ERP components (e.g., the late positive potential (LLP), the N200, and the P300) and ER have been consistently found (Hajcak et al., 2010; Hajcak & Nieuwenhuis, 2006; Lamm & Lewis, 2010; Lewis, Lamm, Segalowitz, Stieben, & Zelazo, 2006; Lewis & Stieben, 2004; Moser, Hajcak, Bukey, & Simmons, 2006).

Measures of Coregulation

Because of the interpersonal nature of the development of ER, developmental scientists often utilize caregiver–child interactions as a means of assessing ER capabilities. Work in this area is founded on the belief that one partner's behaviors and emotions affects the other in reciprocal and dynamic ways, and these complex associations influence children's growing ability to self-regulate emotion (Cole et al., 2004).

To gauge reciprocal regulation of the dyad, infant studies have examined the synchrony and contingency between infants' and mothers' emotional communication and expressive behavior by examining the timing and sequencing of changes in each partner's expression, behavior, and physiology (e.g., Cohn & Tronick, 1989; Feldman, 2009; Field, 1994; Tronick & Cohn, 1989). Crockenberg and Leerkes (2004) demonstrated that adaptive regulation is contingently linked with prior sensitivity behaviors such that in dyads in which mothers responded contingently to their looking away, infants were less distressed than infants whose mothers did not respond contingently; thus identifying contingent maternal responsiveness as a key predictor of ER in infancy. These contingencies have also been examined in the still-face paradigm to assess infant regulation when there is a disruption in the expected course of social interaction (e.g., Braungart-Rieker, Garwood, Powers, & Notaro, 1998; Weinberg, Tronick, Cohn, & Olson, 1999).

In studies of older children, researchers have used previously described laboratory paradigms to assess the social interaction between the caregiver and the child in highly emotionally charged contexts. In a study assessing coregulation during a delay of gratification task, Putnam, Spritz, and Stifter (2002) found that attending away from the forbidden toy most frequently occurred in response to mothers' directives, and when children redirected their attention, mothers appeared to support this regulation strategy through continued distraction. These results emphasized the coregulatory process in which mothers were both affecting their toddlers' regulatory strategies and being affected by their children's behavior. Thus, methods employed to assess the contingent and synchronous interactions between infants' and caregivers' behavior and physiology are well-suited for the measurement of ER.

Multiple Methods and Measures Across Developmental Domains

Last and perhaps most importantly, it is imperative that researchers continue to conduct multilevel research that incorporates multiple methods and measures to assess development within and across levels of child functioning

to better understand the complex behavioral, biological, and social processes implicated in developmental pathways to ER and child adjustment. In their discussion of methodological challenges for future work in emotion regulation, Cole and colleagues (2004) posited that some of the most compelling evidence for the construct of emotion regulation has come from studies that have independently assessed activated emotion and emotion regulation strategies, have analyzed temporal relations among regulatory phenomena, have compared emotion regulation abilities in contrasting conditions, and have used multiple converging measures to demonstrate the organization of emotional regulatory processes. For example, research measuring developmental functioning at various levels might be able to better address how genes influence neural changes in response to emotional stimuli, and how neural changes impact cognition and the production of complex behavior during emotion-eliciting environmental contexts. Moreover, research employing multiple methods to examine within level associations may help clarify and integrate previous work examining behavioral or physiological regulation of emotion. For instance, when individuals encounter situations that require the modulation of emotional arousal, we know that multiple biological systems are enacted (Calkins & Hill, 2007, Thompson et al., 2008). Yet there is relatively little synthesis of theoretical or empirical work addressing the relations among various biological processes and regulatory functioning. Further, Weems and Pina (2010) have underscored the importance of understanding the interrelations of a variety of assessment strategies (i.e., attending to method variance—self-report vs. observation vs. physiological functioning) to improve the assessment of the construct of emotion regulation in psychopathology research. Therefore, measurement of ER at multiple levels of child functioning and the use of multiple assessment strategies may best elucidate the dynamic interplay among multiple developmental processes involved in the regulation of emotion.

CONTRIBUTIONS OF EMOTION REGULATION TO DEVELOPMENTAL OUTCOMES

Considerable research on ER demonstrates it is a powerful mediator of interpersonal relationships and socioemotional adjustment as early as the first few years of life and continuing throughout childhood and adolescence (Thompson & Meyer, 2007). From infancy onward, the practice of early and newly emerging emotion regulation skills leads to greater automaticity and flexibility so that by the time the child is ready to enter an academic setting, greater effort can be directed toward more demanding academic and social challenges, challenges that will change as the child moves through various developmental periods. Importantly, these expanding interactional contexts will place demands that call on the child to use these skills in the service of displaying appropriate social behavior and achieving diverse academic and social goals. Here we consider both normative (social competence, academic performance) and nonnormative outcomes in the form of various presentations of psychopathology.

ER and Developmental Psychopathology

The study of childhood psychopathology has focused largely on two broad sets of difficulties, those characterized by aggression and acting-out behaviors (externalizing problems) and those characterized by anxiety, withdrawal, and depression (internalizing problems; Achenbach, 1991, 1992; Achenbach & Edelbrock, 1983). Here we provide a selective, rather than exhaustive, review of this work, highlighting studies that have addressed specific ER processes and their relation to behavioral outcomes. We address these relations in studies of both normative and clinical samples. Our goal is to highlight the important findings as well as the numerous issues and challenges that illustrate the complexity inherent in the relations between ER and psychopathology.

Externalizing Problems

Much of the early work on ER and psychopathology focused on externalizing spectrum problems, like aggression. Externalizing spectrum problems have likely received more focus because they are more easily observed and may cause greater disruptions in the family, peer, and school contexts. Disruptive behaviors such as aggression, defiance, and temper tantrums are some of the most common externalizing-type behavioral problems seen in children (Beauchaine, Strassberg, Kees, & Drabick, 2002). Traditionally, it was thought that as young children acquire more cognitive, linguistic, and regulatory skills, they are better able to cope with developmental challenges and outgrow these types of problem behaviors (Kopp, 1982; Campbell, 2002). Indeed, much research has shown a normative developmental pathway of externalizing-spectrum behavior problems that peaks during the second year and shows a distinct decline with age (Hartup, 1974; Tremblay, 2000).

Although it may be the case that most children acquire adaptive skills that help them manage challenging

situations in appropriate and constructive ways (e.g., Coie & Dodge, 1998; Tremblay, 2000), for some children, early onset externalizing problems remain stable and lead to more serious maladaptive outcomes such as conduct disorder, attention-deficit/hyperactivity disorder, and juvenile delinquency (Campbell, 2002; Campbell, Shaw, & Gilliom, 2000 for reviews; Cummings, Iannotti, & Zahn-Waxler, 1989).

Such problems are of interest to clinicians and researchers alike because of their influence on concurrent psychological and social functioning (Campbell, 2002), their role in influencing later behavior across social and school contexts (Keane & Calkins, 2004), and their potential to constrain the development of a range of emotional, cognitive, and social skills (Calkins, et al., 2002; Nigg & Huang-Pollock, 2003). For example, in a study of children followed from infancy through late adolescence, Olson and colleagues (Olson, Bates, Sandy, & Lanthier, 2000) found that toddlers who were observed as highly resistant to maternal control received higher teacher ratings of over-activity and aggression across the school-age years. These effects extended into late adolescence such that toddlers who were reported by their mothers to be more difficult and demanding rated themselves as more inattentive at age 17 and were perceived by parents to be higher in aggression. Thus, for some children patterns of aggressive, defiant, destructive, and under-controlled behavior remain stable from preschool to middle childhood (Gilliom & Shaw, 2004),often resulting in more severe maladjustment in adolescence and young adulthood (Olweus, 1979).

The emphasis on ER as a predictor of behavior problems is logical because excessive emotional lability and reactivity, and a lack of behavioral and emotional control, are considered core symptoms for children with externalizing-type behaviors (Gilliom & Shaw, 2004; Keenan and Shaw, 2003). Here we begin by addressing early work examining the relation between ER and broad spectrum indicators of externalizing behaviors and then move to a discussion of more nuanced approaches and differential externalizing outcomes. We focus our review on early development as this is when such problems emerge and become stable, often because they are resistant to treatment.

Some of the earliest work on ER and externalizing spectrum problems focused primarily on the *expression* of emotions such as anger and frustration and used clinical or at-risk samples of children (Barron and Earls, 1984; Bates, Bayles, Bennett, Ridge & Brown, 1991; Campbell, 1990; Shaw, Keenan, & Vondra, 1994). The prevailing perspective on the relation between anger and behavior problems was that children who were quick to anger were more likely to be quick to engage in aggressive and destructive behavior. And, children who are highly reactive to frustration may act aggressively when provoked or aggravated because of their tendency to perceive these provocations as hostile (Vitaro, Brendgen, & Tremblay, 2002).

The view that negative emotion was a prime reason that children engaged in aggressive behavior was in part an outgrowth of temperament theory and research (Rothbart & Bates, 1998; Gilliom & Shaw, 2004). The relation between negative affect and aggressive behavior is not straightforward, however. First, the main effect of anger on aggression is often modest (e.g., Rubin, Burgess, Dwyer, & Hastings, 2003; Runions, & Keating, 2010; White, Jarrett, Ollendick, 2013). Moreover, there is a normative developmental trajectory of early behavior problems characterized by anger and aggression; some children go on to have behavioral difficulties while other children decline in such behaviors (Campbell, 1990; Tremblay et al., 1999). Differentiating these groups of children suggests a more complex pathway from negative emotionality to externalizing-type behaviors such as aggression and defiance.

From a temperament perspective, children's emotional reactivity in combination with their ability to control emotional arousal influences a variety of developmental outcomes (Rothbart & Bates, 2006). Thus, to address the challenge of modest main effects of negative affect or anger on children's adjustment, a number of laboratories began to address the moderating effects of the control or regulation of emotion and behavior. Eisenberg and colleagues (Eisenberg et al., 2001; Eisenberg, Fabes, Guthrie et al., 1996; Eisenberg, Fabes, Karbon, & Murphy, 1996; Eisenberg, Fabes, Murphy et al., 1996; Eisenberg, Fabes, Murphy, & Maszk, 1995; Eisenberg et al., 1994; Fabes, Bernzweig, & Karbon, 1993; Fabes & Eisenberg, 1992) began a series of investigations addressing the interaction of reactivity and regulation in the prediction of social behavior and maladjustment in school age children. Their work consistently demonstrated that children high in anger but lacking behavioral control skills were more likely to display anger and conflict with peers and behavior problems. Subsequent research examining the interaction of reactivity and regulation as predictors of behaviors that fall along the externalizing spectrum focused on younger children. Among preschoolers, caregiver-reported negative emotionality was only related to externalizing behaviors when children were also reported to have lower regulatory skills (Gartstein, Putnam, & Rothbart, 2012). Calkins and colleagues (Calkins et al., 1998) studied a community sample of toddlers and found that the level of frustration

interacted with specific ER strategies (physical venting and attention focused on the object of frustration) to predict conflict with peers. Importantly, all measures from this study were observational, thus providing convergent evidence with prior work relying on parent and teacher report of behavior.

The joint effects of emotional reactivity and emotional control on later externalizing spectrum problems have also been studied during infancy. Stifter and colleagues examined the influence of early ER on subsequent aggressive behavior and found that infants who were highly frustrated and highly regulated were less defiant as toddlers (Stifter, Spinrad & Braungart-Rieker, 1999). More recent work has examined specific dimensions of regulation in infancy as moderators of early emotional reactivity. Belsky and colleagues found that in 15-month-olds, poor attentional persistence moderated the effect of early negativity in predicting poor social competence (Belsky, Friedman, & Hsieh, 2001). Further, Crockenberg and colleagues (Crockenberg, Leerkes, & Jo, 2008) found that attention toward the object of frustration at 6 months moderated the effects of negative affect on later aggressive behavior. Work using observational measures with more diverse samples has validated these early findings (Morris et al., 2010), providing additional evidence to support the general conclusion that ineffective or poor regulation of negative emotional reactivity, particularly attention focused on the object of anger or frustration, is predictive of childhood maladjustment characterized by aggression, acting out, and the display of socially inappropriate behavior.

Although negative emotion has been the primary affect examined in relation to externalizing problems, more recent work has focused on the role of exuberance in the emergence of such problems (Berdan, Keane & Calkins, 2008; Degnan et al., 2011; Stifter, Putnam & Jahromi, 2008). Exuberant children are notable for their positive affect and approach behaviors. A greater tendency to display positive emotions has generally been regarded as adaptive (Eisenberg, Wentzel, & Harris, 1998) and has been associated with greater social competence and fewer behavior problems (Denham, McKinley, Couchoud, & Holt, 1990; Eisenberg, Fabes, Murphy, et al., 1996; Lengua, West, & Sandler, 1998). However, intense positive affect is often associated with greater approach behaviors and thus has been linked to impulsivity and externalizing problems (Cole, Michel, & Teti, 1994; Eisenberg, Fabes, Guthrie, et al., 1996; Underwood, 1997). Similar to work examining negative emotionality, work with exuberant children has found ER abilities to play a role in the association between positive emotionality and behavioral adjustment. Rydell, for example, found that children low in exuberance had fewer externalizing behaviors regardless of how well-regulated they were, whereas among exuberant children, poor regulators were reported to have greater externalizing problem behaviors than children with better regulatory capabilities (Rydell, Berlin, & Bohlin, 2003). Additional work has shown that children high in exuberance who were also observed to have poorer regulation, were also more likely to be rated by parents as aggressive (Dollar & Stifter, 2012). Moreover, exuberant children who displayed higher levels of negative emotion and poorer regulation were rated by their parents as having higher levels of externalizing problem behaviors than exuberant children who could regulate their emotional expression (Stifter et al., 2008) Thus, externalizing problems are perhaps best characterized by poor regulation of affect and behavior that increases children's likelihood of inappropriate social behavior, behavior that may include unregulated approach behaviors associated with peer conflict and aggression.

In addition to a very large literature examining the behavioral manifestations of ER and their relation to externalizing spectrum work, a growing body of work using multiple biological measures has examined neural and physiological ER processes (Dennis & Hajcak, 2009; Hare et al., 2008; Hessler & Fainsilber Katz, 2007; Santucci et al., 2008), and the way these biological mechanisms influence outcomes characterized by externalizing spectrum behavior problems (Granic, Meusel, Lamm, Woltering & Lewis, 2012). There is growing consensus that ineffective biological mechanisms, observed at various levels and involving different systems, are implicated in ER processes that underlie children's social functioning and adjustment (Beauchaine & Gatze-Kopp, 2012; Stifter et al., 2011). Early work with children in this area focused on the role of basal cardiac functioning in the display of emotions (Stifter & Fox, 1990), while more recent work has examined the response of various biological systems under conditions of emotional and cognitive challenge (Calkins, 1997; Calkins, Graziano & Keane, 2007; Granic et al., 2012). Work examining biological response to challenge assumes that underlying neural or physiological mechanisms supports the behavioral processes of ER.

Prior research indicates that there are concurrent relations between externalizing spectrum behavior problems and physiological regulation in response to challenge across childhood, with poor cardiac vagal regulation linked to higher levels of behavior problems (Calkins, 1997; Calkins et al., 2007; El-Sheikh, Harger, & Whitson, 2001). Longitudinal studies also confirm the significance of biological responding to challenge. For example, in

one study, trajectories of ER as indexed by cardiac vagal functioning predicted patterns of externalizing behavior over time, again with poorer regulation predictive of stable externalizing problems (Degnan, Calkins, Keane, & Hill, 2008). It should be noted, however, that within this body of literature there are inconsistencies with regard to optimal levels of cardiac vagal responding, and how vagal regulation during varying types of challenge may be differentially associated with children's adjustment (Beauchaine et al., 2013; Calkins et al., 2007; Hinnant & El-Sheikh, 2013).

Developmental neuroscience confirms the assumption of early work that biological processes may underlie more sophisticated behavioral processes.

Compelling evidence of such a connection has been provided by recent neural work with children. In one study, for example, children who participated in an intervention for externalizing problems displayed changes in neural activity in parts of the brain linked to inhibitory control (Beauchaine et al., 2013). An additional intervention study demonstrated that neural correlates of response inhibition and control differed between children with clinically significant externalizing behavior and an age-matched comparison group. After intervention, however, both neural and behavioral indices of regulation changed for clinical children suggesting more efficient response inhibition in the presence of challenging emotions (Woltering, Granic, Lamm, & Lewis, 2011) These findings suggest that the control processes linked to impulsive, acting-out behaviors originate in neural processes.

Though a substantial body of work established that emotion regulatory process, whether biological or behavioral, may be a critical factor in pathways to externalizing behaviors, consideration has been given to the role that contextual factors play in such pathways. Work that moved beyond main effects models of ER influence on externalizing behaviors initially focused on the caregiving context. Parents can either in the moment or over the longer term affect how children manage their emotions (Calkins, 1994; Morris, 2007; Thompson, 1994). Multiple models of these effects have been proposed: parenting may lead to patterns of ER, moderate existing ER processes, or do both. Much of this work has examined caregiver behavior as affecting ER development through its effect on children's affective reactivity. Thus, caregiving may enhance or undermine the development of important regulatory skills, which, for example, reactive children would have difficulty acquiring otherwise (Braungart & Stifter, 1991; Calkins, 2002; Calkins et al., 1998). Specifically, mothers who are sensitive and responsive may help children who are easily frustrated develop appropriate strategies for managing their affect and social behavior. In contrast, mothers who are intrusive or hostile may exacerbate their children's frustration reactivity, leading to poor regulatory skills, and, in turn, greater disruptive behavior problems (Bates, Pettit, Dodge & Ridge, 1998; Gilliom et al., 2002; Rubin et al., 2003). Thus, there is good evidence that caregiver behavior may support or undermine the development of regulatory skills that increase or decrease the likelihood a child will develop externalizing behavior problems.

Although the moderating effect of maternal sensitivity or intrusiveness may seem straightforward, not all studies find the same direction of effects. For example, one study found that maternal control had a positive impact on children's frustration reactivity (Bates et al., 1998), suggesting that the same level of maternal control may not operate the same way in all contexts or with all children. In some instances (e.g., when danger is present; Bates et al.), maternal control may help dampen children's frustration reactivity and limit the display of disruptive behavior. However, in other situations (e.g., free play; Calkins, 2002), maternal control may exacerbate a negative temperament and increase disruptive behavior. In addition, maternal control may lead to disruptive behavior when children are not prone to frustration, but have strong approach tendencies. Parents may attempt to inhibit the approach behavior, frustrate the child, and increase the likelihood of disruptive behavior (Derryberry & Reed, 1994). An additional challenge to interpreting the large empirical literature on the effects of caregiving on the relation between ER and externalizing is that these reports typically each focus on different aspects of caregiving. Research examining the joint effects of maternal behavior and temperament, for example, reveals that children's frustration reactivity typically predicts externalizing outcomes when mothers are high on control *or* low on positivity (Calkins, 2002; Paterson & Sanson, 1999; Rubin et al., 2003). This makes the explication of the mechanism through which caregiving influences subsequent child problem behavior challenging. Thus, caregiver behavior may have different implications for child externalizing outcomes depending on the child's individual level of frustration reactivity and regulatory capabilities, the context in which such behaviors are observed and the developmental level of the child.

Numerous mechanisms in addition to actual parenting behavior are also likely operating in the developmental processes linking ER and externalizing behavior, including family expressiveness and emotional climate (Morris et al., 2007). Cultural and racial differences in how maternal behavior relates to ER have also been found. For example, Supplee and colleagues (2009) found that

different patterns of ER strategy use were differentially related to externalizing behavior for European Americans and African Americans. These data support the idea that within different cultural groups the expression of emotion and management of emotion may be viewed differently.

In sum, data on caregiver effects for the development of ER and its relation to externalizing behavior suggest that these effects will vary by the age of the child, the specific caregiver behavior, and familial and cultural expectations for the display of emotion. However, caregiving is not the only contextual factor that may influence the relation between ER and externalizing behaviors. Rose-Krasnor and Denham (2009) propose transactional relations between peers and ER, with poor regulatory ability influencing the quality of peer relationships and these peer relationships influencing subsequent behavior. For example, Trentacosta and Shaw (2009) found that ER strategy use in childhood predicted peer rejection in middle childhood, which in turn predicted antisocial behavior in early adolescence. In particular, this study examined use of active distraction and task focus as two replicable strategies typically related to concurrent emotion expression and subsequent behavior. Boys who were unable to engage in distraction during a delay task were more likely to be rejected by peers and more likely to display antisocial behavior. This study helps to identify at least one possible mechanism through which patterns of ER influence adjustment outcomes within the peer context.

To this point, our review has largely considered externalizing behavior problems as broad spectrum and undifferentiated. However, the contribution of ER to different disorders like attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) has also been examined. For example, although there has been a long-standing view of the cognitive or executive functioning deficits in ADHD (Barkley, 1997; Nigg, 2001; Nigg & Huang-Pollock, 2003), more recent work has focused on the role of ER in the disorder (Anastopoulos et al., 2011; Beauchaine et al., 2013; Martel, 2009; Musser, Galloway-Long, Frick, & Nigg, 2013). The pathway from ER to ADHD likely involves failure in the development of basic attention processes used to control impulses and behavior, which have been implicated in the normative decline of more general externalizing problems in early childhood. For example, toddlers with hyperactivity and related behavior problems were rated as high in inattentiveness by both of their parents (Campbell, Szumowski, Ewing, Gluck, & Breux, 1982). In older children, Melnick and Hinshaw (2000) demonstrated that a high-aggressive subgroup of ADHD boys showed significantly less constructive patterns of emotional coping during frustration than both a low-aggressive subgroup and a nondiagnosed comparison group. Recent work has also linked functioning of the ANS, a key biological factor in externalizing broadly construed, to ADHD (Beauchaine et al., 2013; Musser et al., 2011). Thus, the ER difficulties experienced by children with ADHD are likely a function of deficiencies in the attentional systems and neural processes that underlie the disorder.

Like ADHD, ODD is characterized by a distinct cluster of externalizing problems, notably emotional lability, resistance, aggression, and argumentativeness. Thus, problems with the regulation of emotion may be symptomatic of ODD, but may also contribute to it (Dunsmore, Booker & Ollendick, 2013). Conduct disorder (CD) is considered a more serious and persistent pattern of antisocial behavior that is characterized by aggression, destruction of property, more serious rule breaking and deceitfulness. Not only may children with CD display externalizing behaviors similar to children with ODD, but they may also seriously violate the rights of others and society's moral codes. Although theoretical work has implicated deficits in emotion regulation as contributing to ODD and CD, empirical work is relatively limited. In a study of mutual emotion regulation between preschoolers and their mothers, Cole, Teti, and Zahn-Waxler (2003), demonstrated that children who engaged in less mutual positive emotion, more mutual anger, and more emotional mismatches with their mothers had more stable conduct problems than children of other dyads. In a sample of 7- to 9-year-old children at risk for disruptive behavior problems, Duncombe and colleagues (2013) found that parent-reported emotion regulation was significantly related to children's disruptive behavior after controlling for IQ and symptoms of inattention/hyperactivity (Duncombe et al., 2013). Studies with older children and adolescents have shown that inattention, in particular problems with sustaining attention during work tasks, has been linked to conduct disorder (Bellanti, Bierman, & the Conduct Problems Prevention Research Group, 2000; Campbell, Pierce, March, Ewing, & Szumowski, 1994; Olson, Schilling, & Bates, 1999). Further, inadequate vagal modulation of cardiac output, suggesting deficiencies in the physiological regulation of emotion has also been found in children with ODD and CD during middle childhood and adolescence (Beauchaine et al., 2007).

In addition to examining the relations between particular presentations of externalizing problems, recent research has also examined the patterns of problem behaviors over

time. Consistent with a developmental psychopathology framework, theories of externalizing behavior suggest that there are individual differences in developmental patterns of disruptive behavior. Although typically defined a priori, these patterns can be empirically estimated using new statistical techniques, such as semi-parametric mixture modeling (Muthén, 2004; Nagin & Tremblay, 2005). Studies using these techniques reveal empirical support for several patterns of disruptive behavior across early childhood (Shaw, Gilliom, Ingoldsby, & Nagin, 2003; Shaw, Lacourse, & Nagin, 2005). Recent research on trajectories of problem behavior finds that there are multiple trajectories of antisocial behaviors that start early in life (Broidy et al., 2003; Hill et al., 2006; Nagin & Tremblay, 1999; NICHD ECCRN, 2004; Shaw et al., 2003). These trajectories include a normative decline pattern consistent with the findings of longitudinal studies of toddler and early childhood functioning (c.f. NICHD ECCRN, 2004), an early onset pattern, which accounts for the stability of problem behavior across early childhood (Broidy et al., 2003), and an adolescent-limited pattern, which appears to be more transient and less predictive of ongoing difficulties (Moffitt, 1993, 2003).

Although the existence of multiple patterns of disruptive behavior has been supported empirically, the array of factors that might distinguish among these trajectories is less clear. Prior research has focused on several child and environmental factors, including, but not limited to, genes, neural and physiological processes, temperament, family functioning and interaction, and peer relationships and social skills (c.f. Lahey, Moffitt, & Caspi, 2003; Olson & Sameroff, 2009). It is important to note, though, that much of the work on antecedents of early behavior problems has been framed largely in terms of risk factors for problematic behaviors and outcomes, with less emphasis on understanding the mechanisms and processes that link risk factors to outcomes (Rutter, 2003); frameworks that focus on developmental process rather than correlates will likely lead to further elucidation of how risk factors are implicated in the continuity or discontinuity of problem behavior.

Early work has focused on patterns of externalizing problems more broadly, but there is increasing evidence that different patterns of emotional responding and regulation may be involved in different subtypes of externalizing behaviors. Keenan and Shaw (2003), for example, proposed two pathways to reactive versus proactive antisocial behavior. They argued that highly emotional poorly regulated infants when parented in the context of caregiving that was over-responsive to emotions but not demanding would yield a preschooler with difficulties controlling anger and a tendency toward reactive aggression. In contrast, an under aroused infant in concert with overly lax or harsh discipline would yield a toddler unresponsive to punishment and a preschooler who engages in more proactive antisocial behavior like lying, stealing, and fighting.

Another perspective on differentiation of behavior problems has focused on the role that ER plays in altering pathways to subtypes of externalizing problems. In this perspective, ER skills are seen as moderating the early vulnerability to conduct problems that are indexed, for example, by early trait impulsivity (Beauchaine & Gatzke-Kopp, 2012). The assumption here is that ER is a socialized skill that can be a point of intervention for children who are biologically predisposed to impulsive behavior or that under conditions of family emotional lability or negativity may lessen the likelihood that children transition from ADHD symptoms to more severe conduct problems (Beauchaine et al., 2007). Other researchers have taken a different approach and examined the cluster of problems characterized broadly by the term externalizing. Olson and colleagues (Olson et al., 2013) discussed five subcomponents (over aggression, covert aggression, oppositional defiance, impulsivity/inattention, and emotion dysregulation) that they argue compromise-externalizing problems. This taxonomy suggests that ER isn't simply a precursor to disruptive behavior problems, but in fact, constitutes one subtype of behavior problems. Clearly, there is still ambiguity in the field as to whether ER assumes a central role in the etiology of various externalizing disorders, or whether particular deficiencies in ER functioning constitute particular disorders.

In sum, although patterns of emotional control are often seen as symptoms of externalizing behavior problems, developmental research suggests that they emerge earlier than such problems, and in the context of important early relationships, play a causal role in the emergence and maintenance of a range of externalizing type behaviors. Regulation of arousal through both neural and physiological means may be foundational to this process. Important variables that affect the timing, chronicity, and presentation of externalizing problems include the specific strategies that young children rely on in situations requiring the regulation of both negative and positive affect, and the particular strategies that caregivers and peers may rely on when interacting with children learning to manage emotional arousal. Important questions remain about the specific pathways that may be observed behaviorally and the role of neural and physiological processes as precursors or consequences of behavior and behavior problems.

Internalizing Problems

Internalizing-spectrum symptoms primarily include symptoms of depression and anxiety, as well as social withdrawal and somatic changes (Achenbach & Edelbrock, 1981). Historically, developmental research on internalizing symptoms has focused on the early adolescent period and onward (e.g., Angold, Erkanli, Silberg, Eaves, & Costello, 2002; Deković, Buist, & Reitz, 2004; Galambos, Barker, & Almeida, 2003; Kovacs & Paulauskas, 1984; Twenge & Nolen-Hoeksema, 2002), under the assumption that adolescence is a time of risk for such problems. Recent work has shown, however, that rates of internalizing problems during childhood are comparable to rates later in life, with 10 to 15% of US preschoolers meeting diagnostic criteria for a DSM anxiety or depressive disorder at any one assessment (Egger & Angold, 2006; Keenan, Shaw, Walsh, Delliquadri, & Giovannelli, 1997). Such early-onset internalizing problems predict more severe and persistent later mental health problems (e.g., Christie, Burke, Regier, & Rae, 1988; Kasch & Klein, 1996; Kovacs, 1996).

Few studies have examined developmental trajectories of internalizing symptoms before adolescence. To date, these studies typically report no or small increases in mother- and teacher-reported internalizing symptoms from ages 2 to approximately ages 8 to 10 (Colder, Mott, & Berman, 2002; Gazelle & Ladd, 2003; Sterba, Prinstein, & Cox, 2007). However, changes tend to be observed and/or more pronounced in subsets of participants, including children with individual-level (e.g., temperamental) and/or contextual-level (e.g., poor relationships) risks (Gazelle & Ladd, 2003). Given these observations, understanding the relations between ER and internalizing spectrum problems requires studying these associations in childhood as well as adolescence. Like externalizing problems, there has been work that has addressed general internalizing problems, as well as work addressing specific patterns of anxiety and depression. Here, we examine these links in much the same way as we did with externalizing, beginning with early work emphasizing links to temperament and emotion processes and moving to more complex biological and social models.

The early work on the role that emotion plays in internalizing spectrum problems focused on a pattern of behavioral and physiological responding referred to as behavioral inhibition (BI). Children high on BI display fear, withdrawal, and negative affect in response to novel stimuli, have high heart rate and salivary cortisol, and have low heart rate variability (Kagan, Reznick & Snidman, 1987; Kagan, Snidman, Zentner & Peterson, 1999). This pattern of behavior is moderately stable over time (Pérez-Edgar & Fox, 2005). More importantly, though, longitudinal studies indicate that for some children, BI may presage anxiety problems (Chronis-Tuscano et al., 2009; Lahat, Hong & Fox, 2011). Among the processes thought to be implicated in pathways to anxiety among children with BI are internal mechanisms having to do with the regulation of attention and emotion, with the assumption being that children with internalizing spectrum problems have difficulty regulating fear and negative affect (Calkins, 1994; Calkins & Fox, 2002; Degnan & Fox, 2007). Relatively few studies have examined these measures behaviorally with children identified as behaviorally inhibited. The research that has been done does suggest that attention to threat and difficulty controlling attention are characteristic of children with BI (Lahat et al., 2011; Pérez -Edgar & Fox, 2007), and that BI children with these problems are more likely to suppress emotions and display anxiety in adolescence (Pérez -Edgar et al., 2011).

Children with internalizing behavior problems have been sometimes labeled as overcontrolled, implying that they use attention and ER strategies in a hypervigilant way to suppress the expression of negative affect (Eisenberg, Spinrad, & Eggum, 2010). And indeed, among children and adolescents, attentional focus on the source of distress and the suppression of negative emotion have both been linked to higher internalizing behaviors. (e.g., Eastabrook, Flynn, Hollenstein, 2013; Hsieh, & Stright, 2012; Hughes, Gullone, & Watson, 2011; Silk, Steinberg & Morris, 2003). However, the association between ER and internalizing behavior is not that clear, and the processes through which hypervigilance occurs and relates to anxiety are often left unspecified.

Much of the work on ER and internalizing has addressed the role of specific strategies. Following from the adult literature (cf. Dennis, 2007), this work has addressed the role of emotion suppression and attention to threat, as these are strategies that can be observed in children. Recent research has shown that the flexible control of attention, which is critical in successfully regulating emotional arousal, may be challenging for some children. Children who perseverate on some features of the environment to the exclusion of others may be especially vulnerable to increases in experience negative affect and anxiety (White, Helfinstein, Reeb-Sutherland, Degnan, & Fox, 2009). In particular, some children may display an attention bias toward negative/threatening stimuli putting them at risk of developing anxiety due to the increase in fear and arousal that may occur as attention to threat is sustained (Derryberry & Rothbart, 1988; Lonigan, Vasey, Phillips, & Hazen, 2004; Roy et al., 2008). Thus,

it is not surprising that researchers have found rumination to be linked to depression, anxiety, and overall poor mental health in childhood and adolescence (e.g., Hatzenbuehler, McLaughlin, & Nolen-Hoeksema, 2008; Legerstee, Garnefski, Jellesma, Verhulst, & Utens, 2010; Silk et al., 2003).

Although much of the emphasis in the study of ER and internalizing problems has focused on fear and anxiety, other work has examined the relations of negative emotions like anger and sadness to internalizing in children and adolescents (Zahn-Waxler, Klimes-Dougan, & Slattery, 2000). For example, Eisenberg and colleagues (2005) found that elementary school children high on internalizing were prone to greater sadness, low attentional control, and low impulsivity. In another study of children in middle school, Zeman and colleagues (Zeman, Shipman, & Suveg, 2002) found that poor emotion awareness, inhibition of anger, and dysregulated anger and sadness were related to internalizing symptoms. Children who have difficulty recognizing their own negative emotions may have difficulty regulating them, leading to inhibition or dysregulation of negative affect. Although the suppression of negative emotion may help children regulate negative arousal in the moment, failure to express anger and sadness appropriately may exacerbate the experience of those emotions, which in turn leads to greater distress in the form of anxiety or depression (Zeman et al., 2002). In another study conducted by this group, children diagnosed with an anxiety disorder had difficulty managing anger, sadness, and worried emotions (Suveg & Zeman, 2004).

Work with older children and adolescents has addressed the idea that anxiety problems may be a consequence of increased negative affect and distress as well as difficulty coping with that distress (Suveg & Zeman, 2004). For example, some work has examined cognitive reappraisal, thought to be a strategy that helps individuals cope with distressing stimuli (Carthy, Horesh, Apter, Edge, et al., 2010). Children with a diagnosed anxiety disorder were more distressed and less likely to successfully use cognitive reappraisal, particularly when the stimuli they faced were potentially threatening (Carthy, Horesh, Apter, & Gross, 2010).

In addition to the work on internalizing broadly construed and anxiety specifically, recent work highlights the association between ER and the development of depressive symptoms. For example, Silk and colleagues (Silk, Shaw, Forbes, Lane, & Kovacs, 2006; Silk, Shaw, Skuban, Oland, & Kovacs, 2006) have found that for children at risk for developing depressive symptoms, specific types of ER strategies, such as using passive ER strategies, may increase their risk. Yap and colleagues (2007) proposed that the increases in adolescent depressive disorders are a function of increased negative affect that may be observed during this period of time. Specifically, their model proposes that temperament (positive emotionality and negative emotionality) influences the propensity to be negative during this time and that family processes, including family ER and socialization affect adolescent ER.

Although the emphasis in the work on ER and internalizing problems in children and adolescents has focused on negative affect, recent work suggests that positive affect may play a role as well. Recent work in the area of positive psychology suggests that ER strategies for increasing positive emotion are related to well-being and mental health in adults (Fredrickson & Joiner, 2002). In one study, children of depressed mothers who generated positive affect in the face of a delay of gratification task displayed lower internalizing scores (Silk et al., 2006). The ability to control positive affect and utilize it in situations that are challenging may be an alternate ER mechanism that places children at higher versus lower risk for internalizing problems.

To this point, our discussion of ER has largely focused on the use of specific strategies that are thought to lead to increases or decreases in certain emotions and thus contribute to symptomology characteristic of anxiety or depression. However, it is important to note that most studies examine a small number of specific strategies to test the association between ER and problem behavior. A different approach, though it is used in very few studies, is to test whether the use of multiple strategies may in fact be a better predictor of problem behavior. In one study of a community sample of adolescents, 5 different ER strategies were used to differentiate group profiles. The findings indicated that adolescents with a varied repertoire, meaning a high use of several different strategies, displayed lower levels of internalizing problems than those with a more restricted repertoire (Lougheed & Hollenstein, 2012). Flexibility in accessing strategies may be a characteristic that, when in challenging situations, reduces the likelihood of an increase in negative emotions generally.

Thus, the evidence suggests that specific strategies of managing emotion may be related to internalizing broadly and to symptoms specific to anxiety and depression. Similar to the work on externalizing behaviors, important questions regarding the role of ER in patterns of behavior and trajectories of symptomology over time have been addressed. Kim-Spoon and colleagues examined the role of negative emotionality/liability in predicting the trajectory of internalizing symptoms in a high risk sample. Among both maltreated and nonmaltreated children, ER

played a mediating role in the relation between negativity/liability and increases in internalizing symptoms over time (Kim-Spoon, Cicchetti, & Rogosch, 2013).

As with the emergence of externalizing behaviors, internalizing problems develop in the context of social relationships. A number of factors related to parenting and childrearing have been studied (Lahat et al., 2011). A well-known risk factor for internalizing problems is maternal depression (Hammen, 2000), though many children of depressed parents do not develop depression themselves. ER abilities may function as one mechanism that protects children from developing such problems themselves or put children at greater risk if they are vulnerable to such problems by virtue of their own compromised skill at regulating affect (Suveg, Shaffer, Morelen, & Thomassin, 2011).

Environments created by mothers with high levels of internalizing symptoms have been described as emotionally disengaged from the child, with high levels of negative and depressive affect, as well as depressive behaviors and cognitions (Goodman & Gotlib, 1999). Furthermore, anxious and depressed mothers have sometimes been described as over-intrusive and controlling (Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Wood, McLeod, Sigman, Hwang, & Chu, 2003). When coupled with a child's own difficulties in engaging with environmental challenges, maternal depression and anxiety could become overwhelming to the child (Beauchaine, 2001; Crowell et al., 2005), and, thus, further enhance risks for child internalizing symptoms (e.g., Goodman & Gotlib, 1999; Sterba et al., 2007).

Negative and controlling parental behaviors have long been considered a factor in the maintenance of childhood internalizing spectrum problems (Wood et al., 2003). Rubin and colleagues (Rubin, Hymel, Mills, & Rose-Krasnor, 1991) speculated that overcontrolling parents may function to help reduce child distress, but may create overreliance on parental involvement and minimize the opportunity to develop skills to manage independently. Or parental control may be negative in affective tone and serve to increase a child's negative affect. Indeed, in one study, children high on BI who were exposed to high levels of maternal negative control were likely to display more internalizing symptoms in adolescence (Lewis-Morrarty et al., 2012). Feng and colleagues (Feng, Shaw & Moilanen, 2011) examined a moderated mediation pathway from early shyness to ER to internalizing problems in the presence of maternal negative control. In their sample of low income boys they observed that the strategies of active distraction and passive dependence mediated the relation between shyness and internalizing, with active distraction lowering the risk for internalizing and passive dependence exacerbating this same temperament-conferred risk. However, these effects were moderated by the degree of maternal negative behavior; thus mediation depended on the degree of maternal control. Among temperamentally shy children, active distraction only mediated shyness when maternal negative control was low.

Other dimensions of maternal behavior have also been examined as contextual factors that affect ER in children. In a study of 10–12 year old children, attachment to mothers affected indicators of ER including emotional awareness, coping strategies, and biased interpretations of emotion-laden events (Brumariu, Kerns, & Siebert, 2012). These strategies were in turn partial mediators of the relation between attachment and children's internalizing. The argument supports the basic tenets of attachment theory, that secure attachment will lead the child to view the world as nonthreatening, but the mechanism linking attachment to internalizing problems is the way children cope with emotionally charged situations.

In addition to contextual factors that may play a role in the relation between ER and internalizing, work has focused on the biological underpinnings of this relation. Like the work on externalizing behavior problems, much of the work on biological factors implicated in internalizing focused on cardiac indictors of ER. Findings with respect to internalizing-spectrum symptoms and disorders are less consistent than those with externalizing, however (Rotenberg, 2007). Some work suggests that low vagal withdrawal could restrict children's ability to successfully cope with stressors (Graziano & Derefinko, 2013). And indeed, some studies have reported evidence of lower withdrawal scores being associated with more internalizing symptoms (Gentzler, Santucci, Kovacs, & Fox, 2009; Schmidt, Fox, Schulkin, & Gold, 1999). Other work, however, suggests that it may be *high* levels of vagal withdrawal that are associated with dysregulated affect and internalizing-spectrum problems (Beauchaine, 2001; Fortunato et al., 2013; Friedman, 2007; Gazelle & Druhen, 2009; Hinnant & El-Sheikh, 2009). In fact, the highest levels of vagal withdrawal have been reported in young people with particularly severe (Crowell et al., 2005) and also comorbid forms of internalizing symptoms (Calkins et al., 2007). Additional work investigating neural mechanisms of emotion regulation and their relation to internalizing symptoms has shown event-related potentials (ERPs) associated with attention and cognitive control to be different among anxious children compared with typically developing children (Hum et al., 2013). Specifically, anxious children have been shown to have greater mean amplitudes

suggesting that children with internalizing symptoms may exert more cognitive control in anticipation of responding during an emotional eliciting task and their regulation efforts in response to error increase with anxiety induction (Lewis & Stieben, 2004). Thus, the pattern of emotion regulation may depend in part on the underlying biological support mechanisms and in part on the contextual factors that affect emerging ER abilities.

In sum, the work on early ER and internalizing suggests that, like externalizing, child characteristics, such as behavioral inhibition and negative temperament may be the start of a developmental pathway that is mediated by ER processes. How these processes operate in given contexts and as predictors of specific outcomes is still emerging, although the evidence suggests that particular ER mechanisms and potent environmental triggers, like parent psychopathology, are important. Clearly, ER, and in particular, mechanisms of attentional control, are significant factors in the emergence of both internalizing and externalizing disorders, particularly in young children, whose behavioral repertoires may be limited due to the developmental constraints imposed by cognitive and linguistic abilities. Next we address the role that such regulatory processes may play in two other important indicators of child functioning: Social and school functioning. We include these outcomes in our discussion of ER and child adjustment because they are broader indicators of child functioning that are often implicated in the more complex pathways to mental health outcomes.

ER and Social Functioning

Social competence is a multifaceted and dynamic construct that results in positive social experiences with others and the formation of close relationships (Hubbard & Coie, 1994). A large body of literature has identified complex and dynamic relations between social functioning and psychological adjustment and maladjustment both concurrently and longitudinally (e.g., Bornstein et al., 2010; Burt, Obradovic, Long, & Masten, 2008; Kouros, Cummings, & Davies, 2010). Empirical work suggests that social competence may play an underlying role in the emergence and development of internalizing and externalizing behaviors over time (Hinshaw, 1992). Specifically, social competencies may influence child functioning and achievement across multiple developmental domains, and the lack of adaptive social functioning across these domains can prove to be emotionally challenging; increased frustration, anxiety, or depression stemming from highly emotionally charged contexts may result in more aggressive, antisocial, or withdrawn behaviors (Bornstein, Hahn, Haynes, 2010). It is likely that children who do not possess the skills necessary to regulate their emotional arousal have difficulties interpreting and sending clear social messages and consequently experience fewer positive social interactions (Bornstein et al., 2010). Moreover, less social acceptance and increased rejection may also lead to various maladaptive emotional and behavioral responses (Burt et al., 2008). Thus, the degree to which children are able to regulate their emotions has important implications for the development of social competence. Three dimensions central to children's adaptive social functioning have been most commonly associated with ER and psychological well-being: social skills, peer group acceptance, and friendship quality.

Social Skills

Social skills are a foundational component of overall social competence and include the ability to engage in behaviors that benefit others and improve social interactions, such as sharing, cooperating, helping others, appropriately asserting oneself, and responding appropriately in conflict and nonconflict situations (Gresham & Elliot, 1990; Rose-Krasnor & Denham, 2009). These behaviors have been the target of a large body of empirical research across multiple developmental time periods and are found to be associated with children's overall mental health and adjustment in both normative and at-risk samples (e.g., Blandon, Calkins, Grimm, Keane, & O'Brien, 2010; Winsler & Wallace, 2002).

Of the multiple dimensions of social competence, the association between ER and social skills has been most commonly examined. In theory, children who are more competent at modulating emotional arousal are better able to utilize their social skills in a variety of situations (Eisenberg, Fabes, & Spinrad, 2006). Empirical work confirms that greater ER capabilities are associated with increased social skills concurrently and longitudinally, and among young children and adolescents (Carlo, Crockett, Wolff, & Beal, 2012; Eisenberg et al., 1997). Rydell and colleagues (2003, 2007), for example, found that regulation of exuberance, sadness, and anger was positively associated with preschool and elementary school children's ability to engage in positive behaviors such as sharing and conflict prevention at home and at school, and adolescents' ER has been shown to predict prosocial behaviors with strangers, friends, and family (Padilla-Walker & Christensen, 2011).

Friendship

Young children engage in interactions with their peers (Dondi, Simion, & Caltran, 1999), and preschoolers

can develop stable relationships defined by proximity and shared activity (Howes, 1996; Vandell & Mueller, 1980). These relationships can provide companionship and support (Dunn, 2004; Gunnar, Senior, & Hartup, 1984), and are thus an important component of early social functioning (Gottman, 1983). By the beginning of middle childhood, peer relationships take on the qualities of more adult-like friendships such as affective reciprocity, mutual influence, reciprocal recognition of the relationship, a shared history, and relational commitment (Hinde, 1979; Rubin, Bukowski, & Parker, 2006). Friendships high in positive qualities are sources of support (Way, Becker, & Greene, 2006), outlets for intimate disclosure (Newcomb & Bagwell, 1995), and provide companionship (Parker & Asher, 1993). With these relational needs met, high-quality friendships result in youths' positive psychosocial development (Hartup & Stevens, 1999; Savin-Williams & Berndt, 1990). However, friendships that are high in negative qualities, such as conflict and antagonism, are related to higher levels of children's externalizing and internalizing behavior problems (Burk & Laursen, 2005; Sentse & Laird, 2010).

Children's ability to regulate their emotions appropriately and effectively allows for better control of social behavior and facilitates greater communication with social partners. Thus, ER is critical to the development of friendships because ER skills are thought to be necessary for the understanding and interpretation of social interactions, as well as children's behavior in social contexts, thereby shaping the way others perceive and respond to them. Although relatively small in number, there are empirical studies linking ER and friendship. For example, ER has been found to be associated with reciprocal friendships nominations from preschool through young adulthood (Lopes, Salovey, Côté, Beers, & Petty, 2005; Walden, Lemerise, & Smith, 1999). And a recent longitudinal study assessing the relation between ER and friendship quality from ages 5 to age 10, found that increases in mother and teacher-reported ER from age 5 to age 7 was associated with increases in child-reported positive friendship quality and decreases in negative friendship quality from age 7 to age 10 (Blair et al., 2013).

Peer Group Acceptance/Rejection

Another commonly studied dimension of social competence is peer group acceptance and rejection. It has been theorized that peer-rejected children may interpret benign social cues as hostile, leading to a tendency to enact aggressive behaviors (Dodge et al., 2003). Alternatively, peer rejection may lead to behavior problems through truancy, dropout, or association with other deviant peers (Coie, 1990; Dishion, Capaldi, Spracklen, & Li, 1995). Indeed, a number of negative outcomes including early conduct problems, depression, school truancy, and suspension, have been associated with peer rejection in childhood (Coie, Lochman, Terry, & Hyman, 1992; Gazelle & Ladd, 2003; Miller-Johnson, Coie, Maumary-Geremaud, Bierman, & Conduct Problems Research Group, 2002; Woodward & Fergusson, 2000). Relatedly, social withdrawal and peer victimization have been associated with internalizing symptoms such as depression, loneliness, and anxiety (Hodges, Boivin, Vitaro, & Bukowksi, 1999; Hodges & Perry, 1999), as well as externalizing behavior (Blandon et al., 2010; Prinstein & La Greca, 2004).

Children with greater regulatory capacities are thought to be better able to control emotional arousal thus increasing their ability to navigate multiple social settings, cooperate, and positively contribute to peer groups (Eisenberg et al., 2006; Spinrad et al., 2006). Research spanning multiple developmental time periods has highlighted the importance of ER for peer acceptance. For example, 4- to 6-year-olds' emotionality and regulation were related to sociometric ratings of social status concurrently and over time (Maszk, Eisenberg, & Guthrie, 1999). In a study of middle childhood, Kim and Cicchetti (2010) demonstrated that greater reported ER was predictive of higher peer acceptance, and greater peer acceptance was subsequently associated with fewer internalizing symptoms, after controlling for initial levels. Similarly, preadolescents' use of adaptive regulatory strategies, during a laboratory task designed to elicit negative affect were found to be indirectly related to children's antisocial behavior through peer rejection (Trentacosta & Shaw, 2009), such that greater distraction behaviors were associated with less peer rejection, which was in turn related to fewer antisocial behaviors.

Physiological processes of arousal and regulation have also been linked to multiple aspects of social competence. In a sample of preschool children, higher resting vagal tone and greater vagal withdrawal during a negative affect task was related to greater parent-rated sociability (Doussard-Roosevelt, Montgomery, & Porges, 2003). In a similar study, Blair and Peters (2003) found higher resting vagal tone and vagal increase during a cognitive task to be associated with higher ratings of social competence in a preschool Head Start sample. Also, recent research from our longitudinal study indicated that kindergarten children who had better vagal regulation tended to display more adaptive social skills as reported by their teachers and their classmates (Graziano, Keane, & Calkins, 2007). Taken together, these findings provide evidence that

emotion regulation at both a behavioral and physiological level have important implications for children's social functioning and peer relationships.

In addition to the considerable amount of research underscoring the role of social competence in the development of subsequent adjustment and maladjustment, there is also evidence for the reverse association (Hinshaw, 1992; Patterson, Griesler, Vaden & Kupersmidt, 1992). Specifically, psychological maladjustment and deficits in regulatory functioning could undermine social competence such that difficulties processing social behavior, the display of inappropriate or aggressive behavior, or increased anxiety or depression, may disrupt the development of social skills, the formation of healthy peer relationships, and interactions with peers (Bornstein et al., 2010). For example, in early childhood data consistently implicate disruptive and aggressive behavior as a contributor to peer difficulties and rejection (Hinshaw & Lee, 2003), and boys' aggressive and withdrawn behavior during preschool has been linked to social competence in middle childhood (Mesman, Bongers, & Koot, 2001). However, social competence in middle childhood has also been associated with internalizing behaviors in early adolescence (Burt & Roisman, 2010), thus highlighting the inconsistencies in the direction of effects across development.

It is both possible and likely that there are reciprocal relations between social competence and children's maladjustment across time, and one way researchers have begun to disentangle the direction of effects is by utilizing developmental cascades models. The developmental cascades framework allows for modeling complex, dynamic, and longitudinal associations spanning multiple domains (Masten & Cicchetti, 2010), and tests multifaceted hypotheses of developmental theories that aim to represent the complexity of individual development across time and contexts (Cairns, 2000; Magnusson & Cairns, 1996; Masten, Burt, & Coatsworth, 2006). For example, in a 20-year longitudinal study initiating with children 8 to 12 years old, social competence in childhood, as measured by child and parent reported peer popularity and friendship, showed negative longitudinal links to internalizing symptoms in adolescence. Further, social competence in emerging adulthood was negatively associated with internalizing problems 10 years later (Burt et al., 2008; Obradovic, Burt, & Masten, 2010). A similar study investigating developmental cascades among social competence and behavior problems from age 4 to age 14, found lower social competence at age 4 to be associated with more externalizing and internalizing behaviors at age 10, and more externalizing and internalizing behaviors at age 14. Finally, in a preschool sample, Blandon and colleagues found early social skills to have an effect on subsequent levels of externalizing behaviors controlling for previous levels of externalizing behavior, ER, and sociometric nominations. Combined, these results suggest there may be a stronger association from social competence to children's behavioral adjustment across development (Blandon, Calkins, Keane & O'Brien, 2010).

Although researchers are just beginning to untangle the complicated and reciprocal associations between social competence and psychological well-being across development, evidence supporting a significant association is clear: children's ability to utilize adaptive social skills, form and maintain positive friendships, and function appropriately in peer group settings is intricately related to the regulation of emotion and positive behavioral adjustment. Future work addressing the direction, timing and processes involved in these cross-domain relations not only has implications for developmental theory but may elucidate the etiology and consequences of mental health, and identify specific behavioral, social, and emotional processes that can serve as targets of intervention.

ER and Academic Functioning

Successfully navigating the academic environment requires children to function more autonomously and learn important academic and interpersonal skills that contribute to continued academic competence throughout the school years. Meeting increasingly difficult academic demands can elicit frustration, anxiety, fear, and excitement, and the regulation of these emotions may result in a greater use of higher order cognitive processing (e.g., working memory, planning, and attention) (Blair, 2002). Consequently, increased higher order cognitive abilities put children at an advantage and allow for greater attention to classroom tasks, retention of information, efficient learning, and success in achieving academic goals (Graziano et al., 2007).

Poor ER abilities have been linked to deficits in behavioral control such as aggression and antisocial behavior (e.g., Davidson, Putnum, & Larson, 2000; Roberton, Daffern, & Bucks, 2012). Thus, children's ability to control their behavior may be one mechanism through which ER is related to academic success and achievement. The general hypothesis is that children who are emotionally aroused but unable to effectively modulate that arousal in appropriate ways are more likely to display externalizing type behaviors; these behaviors may then lead to decreased academic competence because children are unable to stay academically focused when acting out or

being disciplined for their misbehavior (Hinshaw, 1992; Mile & Stipek, 2006). In contrast, children who are able to modulate negative emotional arousal and demonstrate greater control over their behavior are more likely to stay on task, finish tasks, and focus attention on learning, all of which are needed for continued academic achievement (Breslau, Breslau, Miller, & Raykov, 2011; Moilanen, Shaw, & Maxwell, 2010; Neuenschwander, Rothlisberger, Cimeli, & Roebers, 2012).

Children's academic performance has been shown to be highly stable after the first grade (Entwisle & Hayduck, 1988), and early academic success has been found to be a predictor of later academic achievement (Breslau et al., 2009; Fergusson & Horwood, 1995). Because of this stability, the early childhood period and the transition to school is of particular interest to scientists investigating the associations between ER, externalizing behaviors, and academic outcomes. As children transition from the preschool and home environment to the more academically rigorous environment of elementary school, they are faced with novel academic demands and receive far less external support than they have previously been given (Graziano et al., 2007). Thus, the transition to school can be particularly challenging emotionally, and the ability to regulate emotions and gain increased behavioral control may make the school transition easier and less frightening, in turn setting the stage for greater academic achievement and more adaptive developmental trajectories. In contrast, poor ER abilities and deficits in behavioral control that are linked to aggressive or antisocial behaviors may impede children's ability to function within the classroom, attend to academic demands, and even hinder the student–teacher relationship.

Associations among ER, behavioral control, and academic success in early childhood have been found. For example, Howse, Calkins, Anastopoulous, Keane, and Shelton (2003) found that preschoolers' ER was related to both literacy achievement and math achievement in kindergarten through children's behavioral control (see also Trentacosta & Izard, 2007). Similarly, observed behavioral regulation in emotion eliciting tasks in kindergarten was found to be related to classroom behavior problems and academic performance in first grade (von Suchodoletz, Trommsdorff, Heikamp, Wieberm, & Gollwitzer, 2009), and kindergartners' ER was found to predict fewer parent reported externalizing behaviors, which were associated with decreased academic performance in the classroom and on standardized measures of math and literacy (Graziano, et al., 2007).

There is a small body of research examining the role of both physiological and emotional regulation in school success, broadly defined as social functioning and academic achievement. For example, research examining biological reactivity and regulation has found that these processes are linked to skills necessary for school success. For example, researchers using a different measure of biological reactivity (salivary cortisol) found that preschoolers who evidenced moderate arousal display greater executive functioning (cognitive self-regulation) and were reported by their teachers to have better attentional and behavioral control within the classroom (Blair, Granger, & Razza, 2005). These results support the notion that regulation at the biological level facilitates one's ability to engage and disengage with the environment (Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996), whether that environment consists of social or cognitive challenges, both of which are critical to school success. The question of direction of effects is an important one, though. For example, Blair (2002) proposes that inefficient ER physiologically inhibits the use of higher order cognitive regulation.

There is also support for associations between ER and academic achievement beyond the early school years. A high percentage of school-age children exhibit both externalizing behaviors and low academic achievement (Hinshaw, 1992). However, there is a lack of consensus regarding the direction of effects. One hypothesis is that externalizing behaviors are predictive of later academic difficulties. More specifically, in addition to limiting learning opportunities, externalizing behaviors in middle childhood and adolescence may increase the probability of social rejection or acceptance by deviant peers; thus leading to decreased academic achievement via a disinterest in school or even expulsion (Moilanen et al., 2010; Schwartz, Gorman, Nakamoto, & McKay, 2006). Indeed, empirical studies examining these longitudinal relations suggest that poor ER abilities, and increases in behaviors commonly associated with these regulatory deficits (e.g., hostility, aggression, impulsivity), may undermine later academic achievement. For example, using data from the NICHD Study of Early Child Care and Youth Development, Campbell, Spieker, Burchinal, & Poe (2006) found that children displaying even low levels of physical aggression across childhood were lower in academic achievement at age 9 than children who were not at all aggressive, and ADHD symptoms in sixth grade, as measured by hyperactive and impulsive behaviors, were found to be negatively associated with grade-point average in eleventh grade (Scholten, Rydell, & Yang-Wallentin, 2013). Further,

studies have reported externalizing behaviors to impede children's ability to acquire skills. For example, problem behavior at ages 6 and 11 were uniquely predictive of math and reading abilities by age 17, even after controlling for child, mother, and family characteristics (Breslau et al., 2011). Finally, children's engagement in delinquent behaviors and substance abuse has been found to be associated with lower levels of academic success among adolescents (e.g., Ansary & Luthar, 2009).

ER abilities and behavioral control may also predict academic achievement through the student–teacher relationship. Close and positive relationships with teachers are important for continued academic success such that children with close teacher relationships are more likely to receive positive and helpful feedback, which may in turn increase children's self-efficacy and facilitate a positive view of the academic environment (Birch & Ladd, 1997; Denham, Bassett, & Zinsser, 2012; Pianta, 1999; Pianta & Stuhlman, 2004). And indeed, a number of researchers have found associations between teacher–child relationships and later academic achievement (e.g., McCormick, O'Connor, Cappella, McClowry, 2013; Williford, Maier, Downer, Pianta, Howes, 2013; Zee, Koomen, Van der Veen, 2013).

Because the nature of emotional interactions between students and their teachers are most strongly associated with teachers' perceptions of students (Stuhlman & Pianta, 2002), and there is evidence that teachers have a low tolerance for dysregulated children who are unable to behave in socially appropriate ways (Coie & Koppel, 1990; Roorda, Koomen, Spilt, Thijis, & Oort, 2013), children's ability to regulate their emotions and inhibit aggressive or antisocial behaviors that disrupt classroom activities may result in better student–teacher relationships and subsequently a more positive school experience and increased academic competence (Denham et al., 2003). In alignment with this hypothesis, studies have shown that children who are able to regulate their negative emotions and calm themselves when upset form closer relationships with their teachers and are rated as more well-adjusted in the classroom (Shields et al., 2001). Moreover, kindergartners whose relationships with teachers are characterized by low conflict receive fewer disciplinary actions and are less likely to be suspended through the eighth grade (Hamre & Pianta, 2001). An additional study examining the role of student–teacher conflict in the association between aggression and academic achievement from first to fifth grade, found that changes in aggression significantly predicted changes in the amount of teacher–child conflict, which in turn predicted changes in students' academic achievement. Interestingly, not only did changes in aggression predict changes in teacher–child conflict, but the reverse was also true such that changes in teacher–child conflict also predicted changes in children's aggression, suggesting a complex and reciprocal relation (Stipek & Miles, 2008).

The relation between ER, behavioral control, and academic achievement is more complex than the unidirectional association presented thus far; in addition to externalizing behaviors playing an influential role in children's academic success, academic achievement has also been hypothesized to be a predictor of subsequent externalizing problems. Children who find school more challenging and have a history of repeated failure may become frustrated or unhappy and act aggressively or engage in destructive behaviors, which may then lead to the development of externalizing symptomology (Miles & Stipek, 2006; Zimmerman, Schutte, Taskinen, & Koller, 2013). Academic failure may lead children to develop low self-esteem and a negative attitude toward school, thus prompting the display of negative behaviors (Rutter & Guller, 1983). Miles and Stipek (2006), for example, found that poor literacy achievement in first and third grades was associated with relatively higher aggressive behaviors in grades three and five. An additional study investigating the associations between reading performance and self-reported problem behavior from preschool to second grade found that lower levels of reading performance at the end of first grade were positively associated with more externalizing behaviors at the start of second grade, and lower reading performance at the beginning of second grade was associated with more externalizing behaviors by the end of second grade (Halonen, Aunola, Ahonen, & Nurmi, 2006).

Although the research findings are sparse and less consistent, internalizing symptoms have also been found to be associated with academic achievement. The majority of this literature suggests that objective and perceived academic failures are related to increases in internalizing symptoms such as depression and anxiety. Poor academic performance is often accompanied by low self-esteem and self-efficacy for school related tasks and children may receive negative feedback from parents, teachers, and peers regarding their academic achievements (Cole, 1991; Donnellan, Trzesniewski, Robins, Moffitt, & Caspi, 2005). The inability to regulate negative emotions associated with negative moods, failure, criticism, and negative feedback may in turn result in a negative self-perception and increased internalizing type symptoms. For instance, several studies have linked academic

achievement with subsequent depression (e.g., Huang, 2013; Undheim & Sund, 2005), and anxiety disorders have been consistently linked less decreased academic competence and educational attainment (e.g., Davidson, Hughes, George, & Blazer, 1993; Van Ameringen, Mancini, & Farvolden, 2003).

As with the study of externalizing behaviors, there is also a small body of work suggesting a bidirectional relation. Specifically, internalizing symptoms may underlie subsequent academic functioning. Symptoms of depression such as an impaired ability to concentrate, loss of interest, self-worthlessness, and social withdrawal may hinder cognitive performance and academic achievement if children focus on depressive thoughts or interpretations instead of academic tasks (Hartlage, Alloy, Vazquez, & Dykman, 1993; Kirkcaldy & Siefen, 1998). Jaycox and colleagues (2009), for example, found depression severity in adolescents ages 13 to 18 to predict self-report of academic efficacy and parent report of school functioning 6 months later, even after adjusting for coexisting baseline emotional and behavior problems. Similarly, Obradovic and colleagues (2010) demonstrated that childhood internalizing problems had an effect on adolescent academic achievement over and above the stability of both domains.

Given the evidence supporting bidirectional associations between behavior problems and academic competence, a growing number of researchers have begun to examine transactional and reciprocal relations to gain a more complex and nuanced view of the interplay between both externalizing and internalizing symptoms and academic competence over time. In a study assessing the longitudinal relations between depressive symptoms and academic performance from late childhood to adolescence, Verboom and colleagues (2014) found support for transactional relations such that that for girls, parent and child reported depressive problems were predictive of a decrease in academic performance a year later, and decreases in academic performance were subsequently associated with later increases in depressive problems. However, the reverse was also true. Specifically, greater academic performance was associated with decreases in depressive problems the following year, and decreases in depressive symptoms were associated with subsequent academic performance.

Reciprocal effects between externalizing problems and academic achievement have also been documented. For instance, externalizing problems at fifth grade have been found to be associated with children's math and language grades by the end of sixth grade, and children's math and language grades at the end of sixth grade predicted externalizing problems in seventh grade, which subsequently predicted math achievement and language grades by ninth grade (Zimmerman et al., 2013). Finally, some studies have examined transactional effects of both internalizing and externalizing behaviors and academic achievement in the same model. For example, in a 20-year investigation, externalizing behaviors in childhood were found to be associated with less academic competence by adolescence, which was subsequently associated with increased internalizing problems in young adulthood (Masten et al, 2005). These associations remained significant controlling for within-domain stability, IQ, parenting, and socioeconomic status. Moreover, a similar pattern of findings was found with a different sample, in an earlier developmental time period, and over a shorter period of time (Burt & Roismen, 2010). Additional work has shown externalizing problems at age 6 and age 8 to be associated with less academic competence at age 8 and age 10 respectively, controlling for prior academic competence. In turn, academic competence at age 10 was associated with fewer externalizing and internalizing behaviors at age 11 (Moilanen et al., 2010).

The findings reviewed here suggest that the deficits in regulatory functioning associated with internalizing and externalizing problems impact academic achievement in complex and reciprocal ways. Not only does academic competence predict developmental psychopathology, but there is evidence that maladaptive psychological functioning also plays a role in the development of academic competence. Future work aimed at further disentangling this association across multiple developmental time periods, and identifying important mechanisms, is likely to provide valuable insight for the identification and prevention of problem behavior associated with children's academic competence and achievement.

In sum, the large literature on the relations between child ER and functioning across several distinct but related domains suggests some general conclusions. The regulation of emotions is a multilevel process that integrates biological and behavioral mechanisms. Fundamental to early ER and many later developmental skills and abilities is the control of attention (Zhou et al., 2007). Emotion regulatory ability is both a moderator of affective expression and experience and is moderated by contextual factors like parenting and relationships outside the home with peers and teachers. And, although the regulation of negative affect has been the focus of much work, positive affect and differential strategy use and flexibility in strategy use are also of interest when examining relations between ER and outcomes. Importantly, though, there are clearly multiple

routes from ER to functioning in various domains, and the domains of functioning themselves interact in complex ways to produce constellations of functional challenges for children. The utility of identifying some common routes to specific patterns of dysfunction is critical to intervention and prevention efforts. Identifying critical points of entry and targets of intervention will depend on our field's ability to make sense of the data being generated by an emerging literature and future research. In the next section, we discuss some of the issues that will require attention for this kind of translational contribution to be realized.

INTEGRATION, IMPLICATIONS, AND FUTURE DIRECTIONS: MODELING COMPLEX PATHWAYS BETWEEN ER AND CHILD FUNCTIONING

Despite considerable progress in our understanding that ER is influential in the emergence and/or maintenance of psychopathology and adjustment more generally, many unanswered questions remain about *how* this occurs. This knowledge gap exists, in part, because of a number of conceptual, empirical, and analytical challenges to the study of ER. One solution to addressing these challenges is to apply the *integrative principles* of developmental psychopathology to the specific lingering questions and issues relevant to the study of ER and child outcomes. That is, developmental psychopathology is a framework that requires us to think in an interdisciplinary way about complex processes and outcomes that are predicated upon interactions across multiple levels of analysis. Here we apply this integrative approach to address several important conceptual, empirical, and analytical issues raised by our review.

Conceptual Integration of Developmental Perspectives

There are extensive literatures examining ER from varying theoretical perspectives and considering both intrinsic (Calkins & Johnson, 1998; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Kopp, 2002; Rothbart & Bates, 1998; Stifter & Braungart, 1995) and extrinsic processes (Sroufe, 1996; Morris et al., 2007; Volling, 2001), including a recent burgeoning interest in the biological processes associated with ER (e.g., Blandon et al., 2008; Hessler & Fainsilber, & Katz, 2007; Vasilev, Crowell, Beauchaine, Mead, & Gatzke-Kopp, 2009); however, we, along with others, argue that a broader conceptual framework that incorporates each of these components is needed to better understand the emergence of complex behavior such as ER (Sameroff, 2010; Shonkoff, 2010).

The conceptual integration of biological, behavioral, and social levels of analysis (Gottlieb, 1997), sometimes referred to as a biopsychosocial perspective (Calkins, 2011; Sameroff, 2010), has led to greater appreciation of the complex role of biological processes in transactional models of development. This perspective aims to account for the emergence of patterns of adjustment and maladjustment in child functioning within the context of families and the broader social context, and with an appreciation of the contribution of underlying biological processes. Regardless of the focus of the research or the levels described or assessed, the underlying assumption in this work is the same: genes initiate developmental pathways to complex behavior that are receptive to influences that occur from the cellular level to the level of social context, and all of these pathways and behaviors are candidates for developmental interactions that may influence child outcomes (cf. Cicchetti, Rogosch, & Thibodeau, 2012). Coaction, transaction, and interaction across levels characterize development in a biologically informed model of child functioning (Sameroff, 2010). Thus, a biopsychosocial perspective motivates multilevel research that incorporates biological and behavioral indicators of the factors that may be implicated in developmental pathways to ER and child adjustment (Beauchaine & Gatzke-Kopp, 2012). We use this perspective to highlight additional challenges and future directions in ER research that we believe will clarify our understanding of developmental trajectories important to the origins of mental health or illness, and specifically, to the role that ER processes play in these trajectories.

Developing an Integrated Understanding of Biological Processes

Another direction for future research in ER is to develop a more nuanced and integrated understanding of biological processes that are associated with ER. Much of the work investigating the role of biological systems has focused on the separate physiological correlates of emotion and ER. And, although it is important to understand the implications of each biological system for the development of ER, we believe it is imperative that future work move beyond using traditional correlational approaches and investigating single physiological mechanisms in isolation, and instead incorporate the complexity of biological processes into empirical investigations.

From a biopsychosocial perspective, biological mechanisms underlie transactional associations across multiple levels of child functioning, and a core component of

psychobiological approaches to development is the assumption that genes play an initiating role in developmental pathways (Cicchetti et al., 2012). Although the investigation of genetic variants associated with complex behavioral phenotypes is quickly evolving (Brookes et al., 2006; Goldsmith, Pollak, & Davidson, 2008), studies of the role of genetics in the regulation of emotion remain limited. To explicate the various developmental processes integral to the regulation of emotion, greater attention should be devoted to identifying candidate genes thought to be associated with ER processes. Further, future work designed to disentangle the biological underpinnings of the interactions across behavioral, cognitive, and social levels would provide a richer understanding of the development of ER. For example, how do genes influence neural changes in response to emotional stimuli, and how do neural changes impact cognition and the production of complex behavior during emotion-eliciting environmental contexts?

In addition to investigating how biological processes are related to ER across levels of functioning, it is important that future work examine within level associations in an effort to clarify the integration of multiple biological systems. For instance, when individuals encounter situations that require the modulation of emotional arousal, we know that multiple biological systems are enacted (Calkins & Hill, 2007; Thompson et al., 2008). Yet there is relatively little synthesis of theoretical or empirical work addressing the relations among various biological processes and regulatory functioning. For example, associations have been made between HPA functioning and ANS functioning in the regulation of emotion (Cole, Zahn-Waxler et al., 1996; Stansbury & Gunnar, 1994), but more work is needed to better understand how HPA and cardiac systems work together in affecting children's ability to emotionally regulate.

Of the work considering multiple biological systems involved in the regulation of emotion in adults and children, interesting and important findings have emerged. For example, using functional magnetic resonance imaging (FMRI) and measures of adults' salivary cortisol, Urry and colleagues (2006) found that the ability to emotionally regulate, as indexed by high levels of ventromedial prefrontal cortex activation and low levels of amygdala activation, was related to the steepest diurnal cortisol slopes. These results suggest that the circuitry involved in prefrontal cortex and amygdala functioning enables effective regulation of negative emotion and is associated with the regulation of endocrine activity, which has been found to be important for health and adjustment. Moreover, several studies have explored the association between the sympathetic and parasympathetic branches of the autonomic nervous system as it relates to processes integral to children's ability to regulate emotion (e.g., Beauchaine et al., 2007; Boyce et al., 2001). For example, Stifter et al. (2011) showed that reciprocal sympathetic activation, or increases in sympathetic activity accompanied by decreases in parasympathetic activity, was associated with better ER in the preschool period. In sum, we believe that to broaden our understanding of physiological regulation of emotion, and ultimately move closer to a more unified approach to the understanding of biological processes and their relation to ER across various levels of child functioning, it is important to move beyond studying a single physiological mechanism and begin to measure transactions across two or more of these biological levels.

Integrating Development into Methodology

Clear from our review is that a range of methods is used to assess ER, which likely stems from the varying working definitions of this construct (Cole et al., 2004). However, a challenge to the field is to ensure that we are measuring ER appropriately during different developmental time periods. ER is, of necessity, developmentally defined. Although some children appear to be quite proficient in the use of basic ER skills at a relatively early age, it is clear that across development dramatic growth occurs in the acquisition and display of ER skills and abilities. Because of its dependence on the maturation of prefrontal-limbic connections, the development of emotion regulatory skills is relatively protracted (Beauregard et al., 2004), from the emergence of basic and automatic regulation of biological processes in early childhood to the more self-conscious and intentional regulation of behavior and cognition in middle childhood and adolescence that require and are supported by biological processes (Ochsner & Gross, 2004).

Development from infancy through adolescence is marked by continuous changes and restructurings within and across many domains, including emotional, social, cognitive, and biological development. For our measures of ER to be empirically valid, these reorganizations make it necessary for measures to be sensitive and informed enough to capture developmental changes (Zeman et al., 2007). Because of these developmental reorganizations, the methodology employed is likely to be different across development. It is important to acknowledge that because young children are not capable of accurately assessing and reporting their own emotions (Zeman et al., 2007), ER is often captured through observational and psychophysiological measures in infancy and early childhood.

Alternatively, it is not necessarily developmentally appropriate to be able to observe children's emotion regulatory abilities in middle childhood and adolescence, therefore making self-report measures more appropriate.

Finally, we note the importance of construct validity and comparison across development when designing studies of ER. Although it is imperative to ensure that measures of ER are developmentally appropriate, it is also important to consider if measures of ER can be compared across time. For example, we know that the same situations at age 2 and age 10 cannot be used to successfully elicit anger from children. Yet it is important for the field to consider whether these different measures used to elicit anger and its regulation capture the same process at different points in time. Careful selection of measures and comparisons of both behavior and biology might help ensure that the construct of interest matches the measure employed in a study.

Integrating Negative and Positive Emotions

Although it is widely accepted that ER includes maintaining, enhancing or upregulating, as well as blunting or downregulating, both positive and negative emotions (Cole et al., 1994; Thompson, 2011), the majority of past research has largely focused on the regulation of negative emotion, likely due to its prominence in psychopathology and negative outcomes. Very little is known about the importance of regulating positive emotion for adaptive social and psychological functioning, especially early in development.

In research with adults, there is evidence that upregulating positive emotion is adaptive (Davidson, 2000; Fredrickson, 1998, 2001) because positive emotions are a means of building enduring personal resources, such as physical and intellectual well-being, and social and psychological resources. As importantly, in Fredrickson's undoing hypothesis, which has been empirically supported in research with adults, positive emotions can reverse the effects of negative emotions (Fredrickson & Levenson, 1998; Fredrickson, Mancuso, Branigan, & Tugade, 2000) and therefore, serve as a valuable means of regulating negative emotions. Because there is little research investigating these hypotheses early in development, research is needed to examine if children prone to intense or frequent experiences of negative emotion may benefit from learning to upregulate positive emotion in an effort to downregulate negative emotion. Such findings could have important implications for children at risk for developing various forms of psychopathology in both the internalizing and externalizing realms.

In addition to the need for future investigation of *how* and *when* children's upregulation of positive emotions may promote adaptive social and psychological functioning, it is also important to consider the possibility that some children need to learn to successfully downregulate positive emotions. Although perhaps counterintuitive, recent discussions in the adult literature have acknowledged that more is not always better in terms of positive emotions (Gruber, 2011; Fredrickson, 2013). This may also be true for children. Intense excitement is not always contextually appropriate and may interfere with children's developing self-regulatory systems, increasing their risk for later behavioral and psychological difficulties (e.g., Rydell et al., 2003). Although there has been some discussion of this notion in the developmental literature, more empirical and theoretical work is needed. More research is needed investigating *when* and *how* positive emotion is expressed and regulated, in addition to if and how parents socialize positive emotion, including its regulation, in childhood.

Integrating the Social Context into Studies of ER

Another important area of future ER research is to better understand the intricacies of the transactional nature of the caregiver–child relationship in the development of ER. During the first years of life children make a dramatic transition from relying primarily on the caregiver for the regulation of emotion, to increasing levels of self-regulation. Thus, given young children's minimal self-regulating capacities, developmental theories of ER suggest that the mechanisms responsible for growth in the acquisition of adaptive ER skills are embedded within the interactions between early child characteristics and the relational contexts in which development is occurring. The implication for this perspective is that assessment tools that allow us to capture the dyadic nature of ER may be more informative than tasks that yield information about the individual in isolation.

One way to increase our understanding of the dyadic nature of ER is to assess transactional and bidirectional relations between children and their caregivers from a biopsychosocial framework. Much conceptual work and empirical research supports the view that caregiver behavior affects the development of behavioral regulation of emotion (e.g., Calkins, 2004a; Crockenberg & Leerkes, 2004). However, a challenge for future research is to determine whether caregivers contribute to the *development* of physiological regulation, what mechanisms underlie this association, and how parental influence on children's

physiological functioning affect subsequent dyadic interactions. Theories of self-regulation that focus on underlying biological components assume that maturation of different biological support systems lays the foundation for increasingly sophisticated emotional, cognitive, and behavioral regulation that is observed across childhood (Calkins & Fox, 2002). To the extent that caregivers can provide the support for such physiological control early in development, particularly through the use of physical comforting and support, children should be more successful at using attentional, cognitive, and behavioral strategies to control emotion. In turn, successful physiological, attentional, and behavioral strategies prepare children to engage in interactions with caregivers, facilitating the transactional relationship that reinforces sensitive and responsive caregiving over time. More empirical work is needed to gain a clearer understanding into the complex bi-directional associations between children and their caregivers and to show how these dyadic interactions influence the development of ER process.

In addition to bidirectional relations between caregiving and child ER, we also consider parenting behaviors as regulatory *and* regulated. That is, caregivers must regulate their own behaviors and biological processes even as they are attempting to regulate their children's behavior (Calkins, 2011). For example, an emotional tantrum in a grocery store aisle may elicit anxiety, embarrassment, frustration, or even anger from a parent. To respond sensitively, model appropriate behavior, and provide children with the feedback and support necessary for further facilitation of children's adaptive emotional functioning, parents need to regulate their own physiological arousal, emotions, cognitions, and behavior. We acknowledge that such a theoretical proposition may be difficult to test empirically since the direction of effects may be hard to untangle; however, future work should aim to identify *how* caregiving affects children's ER across multiple levels of child functioning. Further, future research should aim to elucidate the way traits and behaviors of both children *and* caregivers influence multiple developmental processes integral to the development of ER.

Finally, the parent–child relationship is not the only social context in which the development of ER takes place. Once children move into the school environment, teachers and peers take on the partner role in ER processes, by providing feedback and modeling in contexts that may place multiple demands on the child. Given that symptoms of many psychological disorders include aspects of social relationships and relationship functioning, some emphasis on these relations may yield information about the dimensions of ER that are deficient. Thus, assessing dyadic interactions between children and teachers, and within peer groups, is an important future direction.

Incorporating Multiple Indicators of Child Functioning

Our review of the relations between ER and child adjustment is expansive in addressing both psychopathology as well as indicators of social and academic functioning. Clear from this review is that the indicators themselves are related in quite complex ways. Moreover, within the developmental psychopathology literature, the high degree of co-occurrence and comorbidity of symptoms and disorders is also evident. There are at least three challenges here: the challenge of predicting co-occurring problems themselves (e.g., ADHD and anxiety), the challenge of identifying cascading pathways to poor functioning in different domains (e.g., aggression to peer rejection to depression to academic failure), and the challenge of understanding when, where, and how to intervene given these complex pathways.

Co-occurrence and comorbidity have long been an empirical and analytical challenge to the field. Nevertheless, there is good evidence that observations of cascades of problems and the appearance of clusters of symptoms falling into different diagnostic categories are real phenomena reflecting the actual functioning of the individual (Beyers & Loeber, 2003; Lillienfeld, 2003; Masten & Cicchetti, 2010) and have differential prediction to long-term outcomes (Fanti & Henrich, 2010). Acknowledging these likely observations and attempting to unpack them is critical to intervention and prevention efforts. Using ER processes as a window on the child's functioning that is impacting and impacted by experiences in the home, peer and school environments may provide useful signposts for where in the developmental process disruptions to competence are occurring (Blandon et al., 2010).

Integrating Theoretical and Empirical Complexity

Much of the early work on the relations between ER and child functioning relied on relatively simplistic correlations and regressions to examine longitudinal developmental associations. However, the data we have reviewed supporting the relation between ER and child functioning increasingly point to models that capture the complexity inherent in these developmental pathways. Cutting edge research driven by theoretical models designed to capture the multiple levels of functioning and how these change over time requires appropriately sophisticated analytical

techniques. The analytic landscape is rapidly evolving in an effort to meet this need and new advanced statistical techniques are being developed for both person-centered and variable-centered analyses. Within variable-centered approaches, techniques such as repeated measures analysis of variance and regression analyses have been overshadowed by growth curve modeling, path analyses, and time series analyses, with the goal of describing the trajectories of change in variables and identifying multiple predictors of deviation from those trajectories (Laursen & Hoff, 2006). Researchers have also begun to use more person-centered approaches including profile or class analyses to address questions regarding group or individual differences in patterns of development across time and associations among variables at multiple levels of child functioning (Bergman & Magnusson, 1997; Laursen, Furman, & Mooney, 2006; Sterba &Bauer, 2010). Measurement challenges are associated with these techniques, but nevertheless, they offer a means through which researchers can examine trajectories and complex associations among behavioral constructs of interest.

A key point here is that, often, developmental pathway models, which are clearly well suited to the study of ER and child outcomes, predated the statistical techniques to test them (Curran & Willoughby, 2003). This will likely continue to be the case with research on ER as models are modified with new data that, using a developmental psychopathology framework, incorporates multiple levels of analysis over time. Nevertheless, the ongoing development and refinement of statistical methods to test such models is key to further advances in this area.

Adopting an Integrative Model of Control Processes

Implicit, and sometimes explicit in the large body of work on ER is the acknowledgement that emotion regulation is never a purely emotional process (Barret, Fox, Morgan, Fidler & Daunhauer, 2013; Thompson et al., 2008). Emotion regulation draws on fundamental neurological, physiological, cognitive, and behavioral processes, all of which become elaborated and integrated over the course of development. We believe that emotion regulation, and other behavioral and cognitive control processes, are linked in fundamental ways to more basic biological and attentional processes, and have consequences for later-developing and more sophisticated social and cognitive skills. And we, like some of our colleagues (Barret et al., 2013; Blair & Razza, 2007; Eisenberg et al., 2007; Rothbart & Sheese, 2007), embed these processes within the larger construct of self-regulation.

In our conceptualization, we have considered ER as one component of the larger self-regulatory system, which we describe as a system of adaptive control that may be observed at the level of physiological, attentional, emotional, behavioral, cognitive, and interpersonal or social processes (Calkins & Fox, 2002; Calkins & Marcovitch, 2010). Control at these various levels emerges, at least in primitive form, across the prenatal, infancy, toddler, and early childhood periods of development. Fundamental to this developmental process is the maturation of different neural systems and processes that provide a functional mechanism for the behavioral integration we ultimately observe as children mature (Dennis, O'Toole, DiCicco, 2013; Lewis, Todd, & Xu, 2010). Importantly, though, the mastery of earlier regulatory tasks becomes an important component of later competencies, and by extension, the level of mastery of these early skills may constrain the development of later skills. Thus, understanding the development of specific control processes, such as emotional regulation or executive functions, becomes integral to understanding the emergence of other childhood skills and adaptive functioning across developmental domains (Calkins & Fox, 2002).

One task for those interested in the development of emotion regulation is to understand the way rudimentary control processes become integrated into more sophisticated functioning. For example, a putatively emotional task of early childhood, the management of frustration, may be parsed into many smaller challenges for the child, involving processes that are observable in different ways and across different levels of functioning. However, many of these same component processes might also be involved in the successful negotiation of other childhood challenges, which may not have an obvious emotion regulation demand, such as a math test, a soccer game, or a plea to a parent to attend a social event. Because of the challenge in distinguishing whether similar processes that are activated in such different contexts are components of the same or different biological and behavioral systems, in our view, it may be more useful to adopt an approach that considers multiple levels of analysis of self-regulation, rather than isolating emotion regulation and executive functioning from related, or even integrated, control processes (Calkins, 2009; Calkins & Fox, 2002; Posner & Rothbart, 2000). Such an approach has clear implications for empirical strategies for the study of emotion regulation, which are often too narrowly construed to reveal much about the more fundamental processes that may be at the heart of later emerging psychological dysfunction.

One hypothesis that we have been exploring (Howse et al., 2003; Leerkes et al., in press) is that *emotion control processes* moderate trajectories of development of the other more sophisticated control processes. Our rationale for this hypothesis is derived from recent work in the area of self-regulation more broadly construed (Baumeister & Vohs, 2004) and from research in the area of attention development (Posner & Rothbart, 2007). First, at both a neural level and a behavioral level, ER processes recruit and integrate multiple psychological functions (attention, appraisal, affective experience, and motor responding) (Lewis & Steiben, 2004). Thus, it is clear that emotions have the capacity to organize and facilitate, or disorganize and disrupt, other psychological processes (Cole et al., 2004; Gray, 2004), both in the moment, and at the level of the emergence of these skills over the course of early development (Bell & Wolfe, 2004). Second, emotion control processes appear to emerge earlier in development than do cognitive control processes (Blair, 2002). Recent work by Blair and Razza (2007) provides support for such a conceptualization of self-regulation and for the importance of self-regulation on children's early academic skills. Specifically, they found that attentional regulation (effortful control) and cognitive regulation (attention shifting and inhibitory control) were moderately correlated with one another. Even so, measures of both in preschool uniquely predicted academic achievement in kindergarten. To the extent that children understand and control emotions successfully, they have a greater opportunity to attend to, assimilate, and process events in the world around them, thus enhancing both social and academic competence. Therefore, from both a behavioral and a neuroscience perspective, there appears to be support for these relations. However, there may be multiple possible ways control processes influence one another over the course of development; studying the integration of these processes may help elucidate different paths to more sophisticated regulation.

TRANSLATIONAL IMPLICATIONS

Over the last 2 decades, ER research has made important advancements toward understanding the underlying regulatory mechanisms thought to influence childhood adjustment. More longitudinal work across multiple developmental time periods, however, is needed to appreciate the nuances of these associations. For example, currently, there is not a clear consensus whether ER difficulties are a risk factor for the development of psychopathology or whether the onset of psychopathological symptoms makes it more difficult for children to regulate their emotions. Moreover, whether the direction of effects remains consistent from early childhood through adolescence and adulthood is also unknown. Empirical work that can illuminate the direction of effects across development is critical for prevention and intervention work aimed at targeting ER. If poor ER is a risk factor for later psychological symptoms, the goal of intervention and prevention programs should be to increase children's ER abilities. In contrast, if difficulties in regulating emotion are a consequence of psychopathology, tactics used to target ER may be better utilized in treatment rather than prevention (McLaughlin, Hatzenbuehler, Mennin, & Nolen-Hoeksema, 2011).

In spite of the existing challenges to understanding the role of ER in developmental psychopathology, progress has been made integrating the research that has been conducted on ER and adaptive functioning in children and adolescents. For example, there have been a number of emotion-focused preventative interventions targeting children and adolescents' mental health problems. Promoting alternative thinking strategies (PATHS; Kusche & Greenberg, 1994) and the emotion-based prevention program (EBP; Izard et al., 2008), for example, are designed to improve children's ability to discuss, understand, and regulate emotions in an effort to increase social competence and decrease problem behavior.

Programs focused on ER specifically have also been developed and studied. Contextual Emotion Regulation Therapy (CERT), designed by Kovacs and colleagues (Kovacs et al., 2006), aims to identify dysfunctional ER strategies and contextual factors that may maintain maladaptive emotional responses. Although these programs have been shown to be successful in enhancing the development of children's emotional functioning and reducing problem behavior, additional programs derived from a broader self-regulation framework that target multiple regulatory processes (e.g., cognitive, social, emotional, attentional) might further increase the beneficial effects of prevention and intervention. These programs may not only aim to increase understanding of emotion, but also help children reduce physiological arousal, increase attentional abilities, cognitively recognize and reappraise emotional interactions, in addition to strengthening caregivers abilities to assist children during heightened emotional contexts.

Current empirical work has also not provided a clear answer as to how multiple components of ER develop in combination with one another, or what it means for children's adjustment to be competent in one regulatory

domain but deficient in another. For example, it may be that sensitive caregiving can offset biological predispositions to negative emotionality and poor regulation; children's biological predispositions, however, may also make them more or less susceptible to caregiving influences (Kovacs, Joormann, & Gotlib, 2008). Thus, research investigating the associations among regulatory mechanisms in multiple domains is essential for design and implementation of preventative intervention programs because it may highlight specific regulatory processes that, in combination with one another, are more or less impactful to children's adaptive functioning.

Empirical work focused on the specific types of strategies children use to effectively and appropriately manage their emotions also has important translational implications. By eliciting strong emotional responses and examining behavioral techniques that allow children to modulate arousal, research can identify which strategies are most effective during different developmental time periods and across various emotionally charged contexts. Finally, ER research can elucidate the way emotional functioning differs among psychopathological profiles and whether developmental processes that lead to adaptive or maladaptive ER function similarly across levels of severity (Cole & Deater-Deckard, 2009), thereby advancing our understanding of the way ER contributes to the development and maintenance of psychopathological disorders.

Throughout this chapter, we have underscored the way a biopsychosocial perspective may help elucidate developmental mechanisms within the biological, cognitive, social, emotional, and contextual domains that are important for understanding the etiology and development of psychopathology in childhood. We believe that ER research aimed at distinguishing among regulatory processes to acquire more insight into how these processes unfold, while also attempting to understand the way maturation of neurobiological and other physiological systems interact with one another, will be particularly useful in the design and implementation of comprehensive interventions for at-risk children.

CONCLUSIONS

In response to the challenge of Cole and colleagues (Cole et al., 2004) to demonstrate that the construct of ER is scientifically useful, the field of developmental psychopathology provides a clear answer. ER processes continue to be identified as fundamental to functioning across development and vulnerabilities in ER are core features of a range of mental health problems.

Although the study of ER has proven to be fruitful in identifying developmental processes important to social and psychological adjustment, or alternatively maladjustment, there are still fundamental questions about the mechanisms involved in this association, particularly as they relate to identifying pathways to specific deficits and disorders and co-occurring problems. We, along with others (e.g., DelCarmen-Wiggins, 2008), believe that there is still much to understand about the underlying developmental processes, as well as the developmental trajectories, of psychopathology from infancy through adolescence. Research using a biopsychosocial framework may contribute to this endeavor by detecting the mechanisms responsible for psychopathology in children. To this end, we have highlighted the utility of a biopsychosocial perspective for understanding and characterizing how ER confers risk in children and adolescents in several key functional domains. The use of this perspective will encourage researchers to investigate developmental mechanisms across and between multiple levels of child functioning that are fundamental to the regulation of emotion and that protect against or promote mental health risk. Importantly, identifying the etiology and developmental trajectories of mental illness not only will inform preventative interventions targeting ER but also will help in the treatment of mental health issues by determining when and how to best intervene (DelCarmen-Wiggins, 2008).

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CHAPTER 7

Interpersonal Theories of Developmental Psychopathology

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Interpersonal relationships lay at the core of human adaptation, making life worthwhile and keeping individuals fulfilled, successful, and happy. Reflecting this truism, the significance of interpersonal relationships serves as a unifying theme across many disciplines involved in understanding human nature and optimizing adaptation across the life span, including developmental science, social and clinical psychology, social neuroscience, psychiatry, medicine, social work, and education. Across these disciplines, relationships are viewed as a crucial context for development. From early psychological writings to recent theories, a guiding assumption of these perspectives is that humans have a fundamental need for relatedness, as embodied in concepts such as a *need for affiliation* (McClelland, Atkinson, Clark, & Lowell, 1953), *need to belong* (Baumeister & Leary, 1995), and *need for approval* (Rudolph, Caldwell, & Conley, 2005). Thus, historical and contemporary frameworks converge on the theoretical consensus that strong, satisfying, and stable interpersonal relationships play an indispensible function in achieving and maintaining well-being. An unfortunate corollary of this assertion is that failure to fulfill these needs—or fulfilling these needs in unhealthy ways—threatens well-being and places individuals at risk for psychopathology. Indeed, when social conditions impede individuals' ability to meet these core needs, they experience social pain with biological, neural, and psychological sequelae akin to those of physical pain (Eisenberger, 2012).

This chapter explores how psychopathology both emerges from, and contributes to, a disruption in developmentally salient interpersonal processes that interferes with youths' need for relatedness. Whereas some interpersonal theories of developmental psychopathology delve into the early experience of children (e.g., theories of attachment and early deprivation), others emphasize more proximal interpersonal risk (e.g., stress-based and parenting theories). Yet others provide a developmental perspective that integrates across various life stages to explicate intertwined developmental trajectories of interpersonal vulnerability

[1]A color version of Figure 7.3 is available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

and psychopathology. Regardless of focus, these theories highlight the undeniable status of interpersonal relationships as defining contexts for healthy or unhealthy development.

In the first section, we discuss historical perspectives on the role of interpersonal relationships in development and psychopathology. Second, we apply principles of the developmental psychopathology paradigm to provide an overarching framework for considering the interface between interpersonal relationships and psychopathology. We integrate these principles throughout the chapter to illustrate how they can organize, interpret, and enrich interpersonal theories. The bulk of the chapter presents interpersonal theories of psychopathology. Admittedly, our foremost challenge was the inevitable requirement to carve theories at their joints. To be sure, there are some distinct interpersonal theories, many of which revolutionized the fields of developmental and clinical science. Yet, as a consequence of the field's successful push for multifaceted, multilevel, integrative models, we have reached a point where it is common, if not the norm, to contextualize vulnerability within complex conceptualizations that cut across theoretical perspectives and even disciplines. Given this success, we take diverse approaches to summarizing the theoretical state of the field. First, we present theories that focus on particular domains of interpersonal vulnerability, such as parents, families, and peers. Then we describe how interpersonal theories interface with other perspectives by considering factors that moderate or mediate the effects of interpersonal vulnerability on psychopathology. Finally, we present some representative examples of integrative models for particular disorders and we discuss future directions for elaborating these models. In this way, we hope to pay tribute to pioneering interpersonal theories, which have paved the way for continuous advances in theory and research, while also allowing the reader to appreciate the multifaceted complexity of contemporary interpersonal models of psychopathology.

Given the broad scope of this chapter and its theoretical focus, we devote most of our efforts to providing a thorough description of interpersonal theories, with less attention to reviewing supportive empirical evidence. Of course, when evaluating these theories, it is essential to understand their current status in the field. Thus, we provide a limited critical analysis of specific theories and models, but we rely heavily on qualitative, and where available quantitative, syntheses, to which readers can refer for more detailed summaries of empirical investigations. Because the primary aim of interpersonal theories of psychopathology is to account for the precursors and consequences of disorder, we emphasize prospective longitudinal research. Where applicable, we describe the range of methodological approaches used to test the theories.

HISTORICAL PERSPECTIVES ON INTERPERSONAL RELATIONSHIPS AS CONTEXTS OF DEVELOPMENT

Since the beginnings of developmental science, less than 40 years after Darwin's 1859 *Origin of Species*, there has been clear recognition that interpersonal relationships matter for growth and adjustment as well as for conflict and dysfunction. Initially, there was no consensus on which relationships were most important for adjustment, when they were most important, or even the fundamental stance of the developing individual toward a developing society. Over the years there has been a melding of once distinct approaches to form the backbone of contemporary perspectives on interpersonal relationships and developmental psychopathology.

Sigmund Freud and James Mark Baldwin were the most prominent theorists of personality and social development at the turn of the twentieth century, and the influence of both is clear in contemporary thinking. Freud and Baldwin were contemporaries but otherwise not especially similar. For Freud (1916), one's psychic makeup was determined by early experiences; for Baldwin (1897, p. 338), "personality remains after all a progressive, developing, never-to-be-exhausted thing." In Freudian theory, parent–child bonds constitute by far the most influential relationships for development, but to Baldwin all of society impacts the individual. Freudian theory places the core of psychopathology within the person, with antecedents to psychopathology in the intrapsychic and intrafamilial conflicts of the early years, which the adult was basically helpless to change without intensive, professional help. In contrast, to Baldwin the individual was not battered about by conflict, but instead was motivated and in constant interaction with society (Kohlberg, 1982). What makes Baldwin the archetypal interpersonal theorist is that he saw boundaries between people as permeable and viewed life in terms of social networks. Baldwin is perhaps best remembered for what some might call his early version of Piagetian theory. Developmental growth is spurred on by synergies between child and environment, which bend and shape (accommodate and assimilate) to one another's needs. But where Piaget's child is an intellectual abstraction, a cool epistemologist, Baldwin's child is emotional, willful, engaged—"his self is that of a shared social self" (Kohlberg, 1982, p. 312).

As Cairns (1998) notes, Baldwin's (1897) transactional themes are apparent (though rarely cited) in statements by major thinkers across the psychological landscape. Gessell (1928, p. 375) wrote that "even the maladjustments between parent and child are adaptations in a psychobiological sense . . . the roots of the growth of the infant's personality reach into other human beings." The centrality of modeling in social learning (Bandura & Walters, 1959) is a popularization of Baldwin's emphasis on *imitation* as the fundamental interactional process. From ethology, Hinde (1979, p. 23) notes that: "What A responds to in B is in part a function of what A is."

With American psychology increasingly drawn to reductionist behavioral approaches, the transactional models that Baldwin drew out made their reappearance in other disciplines, such as sociological symbolic interactionism (Cooley, 1908; Mead, 1934) and European gestalt psychology. The theoretical underpinnings of social ecological models are in gestalt psychology, the trio of Köffka, Kohler, and Wertheimer who came out of classical German empiricism in perceptual psychology. A hallmark of gestalt is *emergence*, which is top-down in contrast to more bottom-up reductionist approaches. Here, active causal agents are to be found in what can sometimes seem to be more amorphous, intangible higher levels of analysis relative to the concreteness of smaller elements from which larger wholes are built.

By the mid 20th century, a branch of gestaltism became concerned with aspects of social and personality psychology, and to a lesser extent social and personality *development*. In 1939, the psychiatrist Kurt Goldstein wrote *The Organism*, an influential holistic approach to personality that influenced gestalt therapy. A second German émigré, Kurt Lewin (1933), adapted gestalt psychology for the study of social development. In accordance with the basic ideas of the old gestalt psychology, Lewin preferred to see the person and his or her environment as one irreducible unit, called a *lifespace*. The lifespace itself was graded and contoured into different regions of significance to the person, with areas that were easier or more difficult to reach, and that expanded and differentiated with development.

Any interpersonal perspective on the development of psychopathology would have to give a standing ovation to the founder of *sociometry*, Jacob Moreno (Moreno, 1934). Sociometry is the measurement of social relationships; it is a technique for revealing the structure or psychological geography of human relationships, a similar metaphor to that of Lewin's lifespace, which represents a psychological map of the social environment from the perspective of a motivated person, or Baldwin's (1897, p. 484) *socionomics*—"the science of the relation of social life to its environment, including other social groups." Sociometry was a way of making visible the intangible social forces, operating at the levels of friends, enemies, and peer group structures, that influence adjustment. The care and meticulousness of the sociometric approach provided a method for describing and understanding the pattern of social influences that may impinge upon the person in larger social units beyond the family. With the coming of age of more sophisticated social network techniques, principles of sociometry are still highly relevant to studying the pattern of relationships in which individuals participate over time.

By the advent of World War II, psychoanalysis had clearly become the dominant framework of interpersonal relationships, development, and psychopathology. Psychoanalytic theory was incorporated into empirical developmental models by forming hybrids with Hullian drive-reduction, leading to social learning theory, and with ethology, leading to attachment theory. As the pages ahead will show, both social learning (e.g., Patterson, 1967) and attachment (e.g., Bowlby, 1969) theories have been enormously influential as two dominant interpersonal frameworks on developmental psychopathology.

The foundational psychoanalytic theories of the era before World War II and behavioral theories of the 1970s focused on early experience in the family as the causative agent for later psychopathology. However, it was always clear that relationships beyond the family, and at any point in the life course, could lead people to great personal fulfillment or to deep misery or anger. Although some of these impactful relationships involve a level of hierarchy and age differential that can also characterize family relationships, most other relationships beyond the family involve no such role-defined or hierarchical distinctions, and are so said to involve peers. A peer is an equal, of the same social standing as oneself (Hartup, 1983). It is this aspect of equality that allows for the healthy conflict and cognitive-moral growth perspective of Piaget (1932), opportunities for positive intergroup relationships as specified in contact theory (Allport, 1954), and the ability to develop empathy and perspective-taking, a sense of the generalized other (Mead, 1934). How we get along with peers is a key indication of how the individual fits into society. Of course, then, troubling aspects of peer relationships form a breeding ground for psychopathology.

Henry Stack Sullivan, a neopsychoanalytic psychiatrist, pointed out as early as the 1940s that peers could be as great an influence on development as parents, and that, in fact,

the right kind of friend, or chum, in preadolescence could smooth out the warps and woofs of ineffectual parenting. In Sullivan's eyes, as reflected in his 1953 posthumous volume *The Interpersonal Theory of Psychiatry*, the friend is the most exquisite of all human relationships. Even before Harlow claimed to be capturing the origins of love in the rhesus monkey's spring toward the cloth mother (Harlow & Zimmerman, 1959), Sullivan wrote that full-blown love requires that kind of secure relationship to a same-sex juvenile peer, characterized by the stance of equal status and a deep empathy and support. Sullivan's work heralded a rapprochement between symbolic interactionism (i.e., views of the generalized other and how they impinge upon the self) and psychoanalysis (Cairns, 1998), and he opened up the way for considering interpersonal influences beyond parenting in the early years for development and psychopathology.

Urie Bronfenbrenner (1979), who began his career in the sociometric perspective of Moreno (e.g., Bronfenbrenner, 1944), presented an integrative perspective that grants precedence to neither family nor peers but considers the unification and interplay among social-ecological contexts. The major tenet of Bronfenbrenner's person-process-context model is that individual development is situated in a system of contexts that are nested within one another. Most developmentally proximal to the individual is a microsystem, which involves face-to-face interactions and relationships between an individual and others in the social environment (e.g., parent–child, peers) that directly affect the developing individual. Proximal microsystems are linked together in mesosystems that constitute the interactions between settings in which the developing individual is situated. Individuals are also situated in exosystems that include interactions between proximal and more distal systems that may operate indirectly on the individual (e.g., parents' work environments and experiences). Micro, meso, and exosystems are situated within macrosystems that encompass cultural beliefs, opportunities, and knowledge structures. Finally, at the broadest level, chronosystems situate macrosystems within historical time and capture processes that can account for cohort effects in development. These systems were heuristics by which psychological events occurring in multiple contexts could be linked from the point of view of growth of the developing child. In this way, social-ecological models are inherently cross-contextual, dealing with peer, family, and more distal (e.g., society) contexts. At the time Bronfenbrenner first proposed his model, he characterized the study of human development to that point as being the "science of the strange behavior of children in strange situations with strange adults for the briefest possible periods of time" (Bronfenbrenner, 1977, p. 513). One of the chief contributions Bronfenbrenner made to developmental science was to situate understanding of development as being embedded within multiple real-life interpersonal contexts. The core of ecological models comes from the transactional, gestalt ideas of Baldwin and Lewin. Ecological models continue to be updated (Sameroff, 2014) and represent many contemporary principles of developmental psychopathology within an interpersonal context.

PRINCIPLES OF DEVELOPMENTAL PSYCHOPATHOLOGY WITHIN AN INTERPERSONAL CONTEXT

The field of developmental psychopathology (DP) provides a comprehensive framework for conceptualizing the role of interpersonal relationships in the development of psychopathology. Integrating key principles of this perspective can enrich interpersonal theories, generate novel hypotheses, stimulate innovative and sophisticated research paradigms, and organize the interpretation and integration of empirical findings. Below we discuss four principles of DP that serve as useful guides for model-building and empirical inquiry in the context of interpersonal theories of psychopathology.

Intersection of Normative and Atypical Development

The DP paradigm seeks to elucidate the intersection of normative and atypical development (Cicchetti, 1993; Cicchetti & Cohen, 2006; Cicchetti & Toth, 2009; Rutter, 2014). Within an interpersonal context, this principle fosters questions such as (1) How do challenging social experiences undermine typically developing interpersonal competencies and age-appropriate relationships to heighten risk for psychopathology? and (2) How does the experience of psychopathology disrupt emerging interpersonal skills and relationships? To evaluate youths' adaptation, we must understand which stage-salient tasks emerge across development and how failure to accomplish these tasks sets the stage for psychopathology.

As will be discussed within each section, children progress through various stages in their relationship development, each of which requires the acquisition of more advanced skills and presents new expectations and challenges. From infancy and early childhood into middle childhood, youth must amass skills for the independent coordination of interpersonal interactions and

the formation of more complex peer relationships. During adolescence, youth must successfully navigate the process of individuation from the family and potential conflict arising from balancing relatedness within the family and peer group. Entrance into dating and romantic relationships presents a host of challenges as youth learn how to manage emotional intimacy and sexual activity. Psychopathology may arise from a failure to effectively negotiate these tasks (e.g., inability to form healthy peer relationships), untimely—either too early or too late—progression through stages (e.g., early entrance into romantic relationships), or excessive focus on one task at the expense of another (e.g., exclusive reliance on peer groups accompanied by extreme detachment from the family). In turn, psychopathology early in the life course likely undermines future task achievement. Considering normative development also highlights questions such as whether (and why) there are age-related changes in youths' interpersonal risk for psychopathology as well as whether (and why) certain developmental stages are linked to susceptibility to certain disorders (Rutter, 2014).

Transactions Between Children and their Environments

The DP paradigm also emphasizes how characteristics of children and their environments dynamically transact over time to shape the course of development (Rutter, 2014). Transactional models hold that children not only are passive recipients of experience but also play an active role in selecting, shaping, and constructing their environments, resulting in feedback loops that stimulate continuous structural reorganization and change (Cicchetti, 1993; Rutter, 2014; Sameroff, 2014). Such models have a long history in the field of developmental psychology. For example, Scarr and McCartney (1983) suggested that children engage in *niche picking or niche building*, selecting and creating environments that best match their natural proclivities. Caspi and colleagues (1989) proposed that children shape their environments through processes of *cumulative continuity*—in which behaviors are sustained across time by accumulation of their own consequences—and *interactional continuity*—in which children's behavior elicits sustaining responses from others during social interactions. Boyce and colleagues (1998) used the term *mutual determination* to describe the continuous exchanges between individuals and their social contexts that guide the course of development.

Capturing these transactional perspectives, the contemporary notion of developmental cascades (Masten & Cicchetti, 2010) proposes that the progressive and cumulative collection of experiences and behaviors drives development, such that early adaptation creates lasting changes with profound effects on subsequent health. Cascade models trace the developmental mechanisms through which risk factors affect outcomes over time, and examine spillover from one domain to others. Within an interpersonal context, early adverse environments or skill deficits can propel children along increasingly maladaptive pathways; risk for psychopathology escalates as the effects of early difficulties snowball into more severe intra- and interpersonal challenges. Once psychopathology emerges, this risky pathway becomes increasingly canalized and resistant to change.

As transactional models gain traction in the field, scientists are exerting significant efforts toward identifying the precise ways in which children contribute to their environments. In this vein, it has long been proposed that gene-environment correlations (rGE) account for individual differences in children's creation or selection of their environments (Plomin, DeFries, & Loehlin, 1977). *Passive effects* models assert that genetic factors shared by parents and children shape the environment in which children develop (e.g., exposure to certain parenting styles or family stress), which then influence youth development; that is, youth inherit not only genes but also genetically mediated environments. *Evocative effects* models assert that genetically mediated characteristics (e.g., temperament) elicit interpersonal reactions that promote and maintain youth outcomes. *Active effects* models assert that genetic liability induces characteristics (e.g., social motivation) that influence how youth select or shape particular environments. Passive effects likely wane, and active effects likely strengthen, across development as youth gain increasing control over their environments (Scarr & McCartney, 1983). A mounting body of evidence supports rGE as a contributor to social experience (for a review, see Rutter, 2014), with recent research on epigenetics suggesting even more complex processes whereby environmental forces actually drive gene expression (Meaney, 2010). Such child–environment interplay should certainly be kept in mind when considering the interpersonal context of psychopathology.

Interacting Systems and Levels of Development

According to a DP perspective, development is energized by synergistic interactions among multiple systems (biological, cognitive, emotional, and behavioral) and levels (personal, interpersonal, societal) of adaptation (Cicchetti & Cohen, 2006; Rutter, 2014). Within an

interpersonal context, multiple characteristics of youth and their environments determine how experiences are encoded, resulting in complex and continuously evolving interactions among genetic, biological, psychological, social, and cultural risk and protective factors. Consistent with this principle, interpersonal theories of psychopathology must consider how various factors jointly determine developmental trajectories. Developmental scientists have proposed several models of *person–environment (PxE) interactions* to explain individual differences in sensitivity to social contexts (Figure 7.1). Broadly, these models take a diathesis–stress form, wherein the interaction between individual susceptibility and stressors determines risk for psychopathology (Sameroff, 1987). However, these theories differ in their precise predictions about the nature of this interaction.

According to *vulnerability* models (Figure 7.1a), such as the dual risk (Belsky, Bakermans-Krannenburg, & van IJzendoorn, 2007; Sameroff, 1987) or stress-amplification (Rudolph & Flynn, 2007) models, heightened sensitivity predisposes children to the harmful effects of stress, making them more vulnerable to psychopathology over time. According to *plasticity* models (Figure 7.1b), such as the biological sensitivity to context (Boyce & Ellis, 2005; Bush & Boyce, 2014) or differential susceptibility (Belsky et al., 2007) models, individual differences in sensitivity influence children's reactivity to both adverse and beneficial contexts. Specifically, sensitivity to context confers health risks in the context of adversity but health benefits in the context of support. According to *stress–sensitization* models (Monroe & Harkness, 2005), early adversity and its consequences for individual sensitivity reduce an individual's threshold for reactions to subsequent stress, such that less severe stress is required to trigger psychopathology in youth with than without a history of adversity (Figure 7.1c). According to *stress–inoculation model*s (Garmezy, 1986; Rutter, 2014), adversity actually buffers or steels youth (e.g., through the development of strong coping skills) against the debilitating effects of subsequent stress—that is, youth with a history of adversity would show stress resistance or reduced stress reactivity (Figure 7.1d).

Understanding PxE contributions to psychopathology can be enhanced by considering the various ways in which individual reactivity to the environment is translated into risk or resilience. Most theory and research on interpersonal models of psychopathology assume a vulnerability perspective; however, mounting evidence implicates plasticity and stress-sensitization models, suggesting the need to broaden current perspectives to consider variability in how individual differences arise. A broad array of individual difference variables have been investigated as possible determinants of youths' reactivity to interpersonal

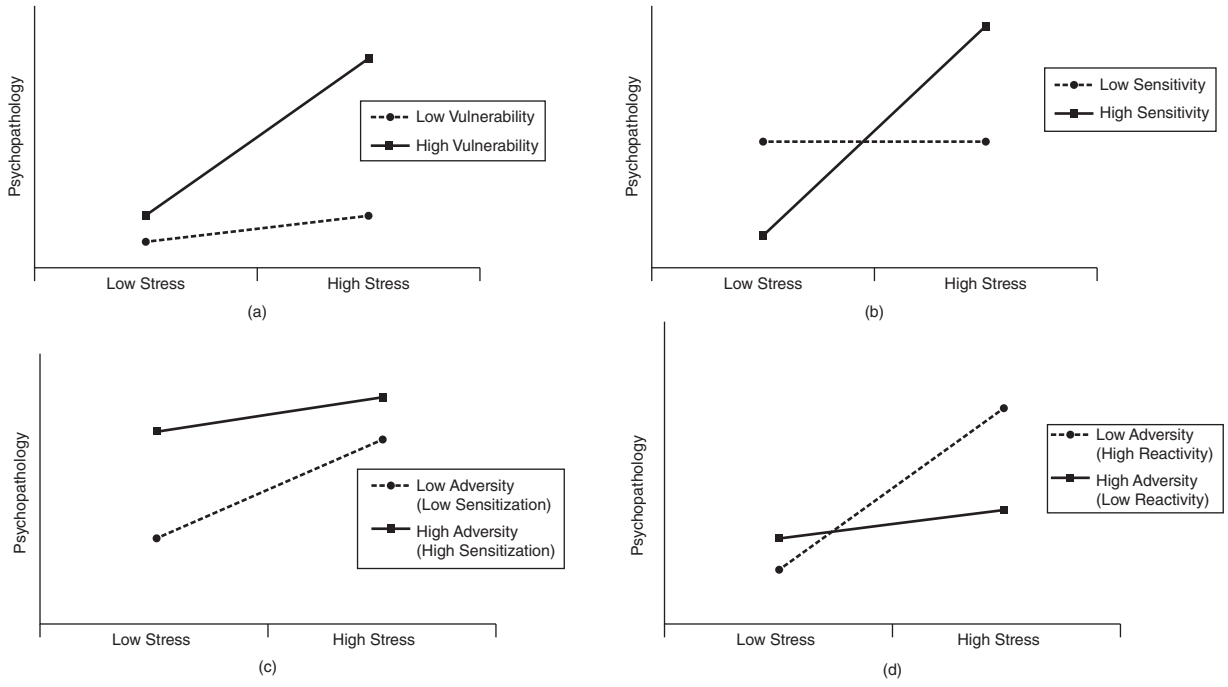


Figure 7.1 Models of person–environment (PxE) interactions. Childhood adversity and youth depression: The role of gender and pubertal status. *Development and Psychopathology, 19*, 497–521. *Source:* Adapted from K. D. Rudolph & M. Flynn, Childhood adversity and youth depression: The role of gender and pubertal status, *Development and Psychopathology, 19*, 499, 2007.

adversity, including genetic variability, temperamental and biological characteristics, cognitive styles, and coping and emotion regulation processes.

Continuity and Discontinuity in Development

Finally, the field of DP espouses an organizational approach, assuming that development unfolds in a predictable way as earlier experiences and abilities are re-organized into more complex behaviors over time. Key to this perspective is appreciating not only homotypic continuity (similarity in the overt expression of adaptation) but also heterotypic continuity (similarity in the underlying organization of adaptation) over time (Rutter, 2014). Thus, both competence and maladaptation are carried forward across development in a continual process of hierarchical integration (Cicchetti & Schneider-Rosen, 1986). From an interpersonal perspective, continuity may be expressed in terms of predictable patterns of functioning within developmentally salient relationships. That is, optimal social health will differ dramatically when considering how youth function within different relationship domains at different life stages, but there will be predictability in youths' general manifestation of competence or incompetence as related to the accomplishment of stage-salient interpersonal tasks.

Despite this emphasis on developmental continuity, the DP perspective also allows for discontinuity, perhaps prompted by significant normative transitions (e.g., progression through puberty) or non-normative challenges (e.g., death of a parent). That is, development unfolds in a lawful and predictable, but not deterministic, manner. Discontinuity can be driven by the acquisition of new competencies (e.g., acquiring self-regulation skills) or by critical events or changes in social contexts that either provide new resources (e.g., acquiring a new peer group during a school transition) or undermine existing resources (e.g., losing support following a romantic break-up), thereby creating turning points in development. The fact that early interpersonal experiences are not necessarily deterministic—for better or worse—of subsequent development is reflected in the concepts of *multifinality* (when similar risk factors contribute to varying outcomes) and *equifinality* (when varying risk factors contribute to similar outcomes; Cicchetti & Rogosch, 1996). Consistent with multifinality, children exposed to highly similar early adverse interpersonal environments can follow divergent pathways, ranging from adaptation to diverse types of psychopathology. For instance, youth exposed to maltreatment during childhood may be susceptible to later anxiety, depression, or externalizing disorders or alternatively may show resilient outcomes. Consistent with equifinality, different interpersonal experiences can lead to similar long-term outcomes. For instance, antisocial behavior in adolescence may stem from harsh parenting, chronic exposure to peer victimization, or affiliation with deviant peer groups. Interpersonal theories of psychopathology must incorporate this multiple pathways perspective that accounts for the possibility of both continuity and discontinuity across individuals, contexts, and time and must explain the mechanisms underlying stability and change (Rutter, 2014).

GENERAL INTERPERSONAL THEORIES OF DEVELOPMENTAL PSYCHOPATHOLOGY

Theories Focused on the Parent–Child and Family Context

Because families are among children's most powerful socializing influences, many notable theories describe their contribution to the development of psychopathology. Families exert an influence through both direct (explicit) and indirect (implicit) pathways. With regard to direct pathways, parents serve as socialization agents who encourage children to think, feel, or act in particular ways and who exert control over children's experiences and opportunities. Children also learn from observing and modeling their family members and receiving reinforcement to act in particular ways. With regard to indirect pathways, families implicitly convey messages about children (e.g., whether they are competent, worthy, ineffective) and the world (e.g., whether it is supportive, rejecting, dangerous) through the nature of parent–child relationships and the emotional quality of socialization efforts. Both direct and indirect pathways can help to explain the transmission of interpersonal vulnerability and psychopathology across generations. Parent- and family-oriented theories variously focus on specific aspects of the parent–child bond, more general parenting contexts, and the broader family environment. Each of these dimensions is considered in turn.

Attachment Theory

Theoretical Underpinnings. Originally developed by John Bowlby (1969, 1973, 1980) and elaborated by Mary Ainsworth (Ainsworth, Blehar, Waters, & Wall, 1978), attachment theory provides one of the most comprehensive and undoubtedly influential frameworks for understanding the normative emergence of social bonds as well as individual differences in patterns of social and emotional development (for reviews, see Cassidy & Shaver, 2008;

Roisman & Groh, 2011). Beyond its theoretical propositions regarding the normative unfolding of development, attachment theory has been widely invoked to explain how disturbances in early caregiver–child bonds can presage the emergence of psychopathology (for reviews, see Cicchetti, Toth, & Lynch, 1995; DeKlyen & Greenberg, 2008; Kobak, Cassidy, Lyons-Ruth, & Ziv, 2006).

Consistent with its evolutionary heritage, attachment theory proposes that infants engage in relationship-enhancing behaviors (e.g., orienting, crying, clinging) whereas their caregivers engage in complementary attachment-promoting behaviors (e.g., touching, holding, rocking); these behaviors presumably are guided by instinctive drives and confer benefits for survival as they maximize proximity to and protection by caregivers in the face of separation or threat. For humans, effective synchrony between these behaviors cultivates a secure caregiver-infant bond, which in turn fosters adaptive patterns of relatedness throughout the life span. Specifically, Bowlby (1969, 1973, 1980) believed that a secure attachment evolves through caregivers' display of sensitive, consistent, and warm responses to their infant. Through this contingent responsiveness, the attachment figure serves as a secure base by promoting exploratory behavior in the infant. Moreover, a secure infant demonstrates separation protest by resisting separation from, and seeking proximity to, the attachment figure. In turn, the attachment figure represents a haven of safety to which the infant can return when distressed. Thus, the attachment bond serves as a behavioral control system that organizes and regulates infants' reactions to the environment, particularly under conditions of threat or stress. Through this bond, the infant learns to balance support seeking with self-reliance and to develop independent strategies for the regulation of emotion. In a complementary fashion, when caregiving conditions are compromised through rejecting, inconsistent, distant, or abusive parenting, the infant fails to develop a sense of security and trust that lays the foundation for healthy adjustment. Rather than using the caregiver as a secure base, the infant avoids or resists comfort by the caregiver or does not develop a coherent, effective strategy for managing negative emotions and stress (Ainsworth et al., 1978).

Developmental Significance and Change. Bowlby theorized that this foundational attachment bond influences development across the life course. To account for this developmental continuity, he proposed that early caregiver–infant ties are internalized in the form of internal working models (1973, 1980) or cognitive representations of the attachment figure, the attachment relationship, and the self in the context of this relationship. The presumption is that as children gain more sophisticated cognitive and language abilities and an accompanying capacity for abstraction, the attachment system transforms from an overt and concrete behavioral manifestation of the infant's response to immediate threat into a symbolic consolidation of repeated experiences that guides the interpretation of ongoing interpersonal encounters as well as expectations for future relationships (Bowlby, 1973; Cicchetti, Cummings, Greenberg, & Marvin, 1990; Thompson, 2008). These working models most likely function outside of immediate awareness and may filter or distort incoming information, thereby increasing their resistance to change. In this way, internal working models serve as the vehicle through which early experiences are carried forward across the life course and trigger the recapitulation of early interpersonal themes in the context of developmentally salient relationships.

To illustrate this continuity, an infant who receives consistent comfort and support from his or her attachment figure would (1) develop an image of others as accepting and dependable; (2) value close relationships; and (3) perceive the self as worthy of love (Cassidy, 1988). This securely attached child would be competent and effective when faced with challenge and would cultivate close and trusting relationships with others. In contrast, an infant who experiences unpredictable or hostile caregiving would (1) develop an image of others as unavailable or rejecting; (2) deny the significance of close relationships; and (3) perceive the self as worthless or incompetent (Cassidy, 1988; Weinfield, Sroufe, Egeland, & Carlson, 2008). This insecurely attached child would be overwhelmed and ineffective when faced with challenge and would develop either an avoidant or hostile approach toward the social world.

By attempting to explain the changing nature yet enduring effects of attachment, as embodied in the construct of internal working models, attachment theory epitomizes the organizational approach to development (Cicchetti et al., 1990). Although the early caregiver–infant bond presumably serves as a profound organizational force across the life course, the manifestation of healthy (secure) or unhealthy (insecure) attachment shifts in developmentally meaningful and predictable ways as related to stage-salient tasks and competencies. Indeed, contemporary perspectives consider the diverse nature and consequences of attachment across developmental stages as it transforms in both its form and its organization (Cicchetti et al., 1990). First, the target of attachment-related cognitions and behaviors may shift or spread across development,

with peers and romantic partners taking on prominent roles as attachment figures. Second, although the function of attachment behaviors remains constant, the overt expression of attachment organization will vary over time. Third, the attachment system may increasingly integrate behavioral, cognitive, and affective components. As such, a healthy attachment may be expressed as secure base behavior with caregivers during infancy, confidence in peer availability during middle childhood, comfort with intimacy in romantic relationships during adolescence, and provision of sensitive caregiving to one's own child during adulthood.

Reflecting this developmental perspective, individual differences in attachment have been conceptualized, measured, and classified in varying ways at different life stages. These approaches are described in detail elsewhere along with critiques of their construct validity and utility for testing key theoretical propositions of attachment theory (Cassidy & Shaver, 2008; Roisman & Groh, 2011). Here, we briefly summarize each approach for the purpose of providing a methodological overview and introducing key concepts and terms as a basis for later discussion.

Ainsworth and colleagues (1978) developed the first research paradigm and classification system for studying variation in infant attachment. The Strange Situation involves a series of increasingly stressful separations and reunions between infants and their caregivers; coding of these episodes focuses on the organization of infants' responses in the presence of the caregiver (engaging in secure base behaviors, such as exploration) and during reunion following separation (engaging in safe haven behaviors, such as proximity seeking and effective use of caregiver comfort). Secure infants show exploratory behavior in the caregiver's presence, seek out their caregivers when distressed (following separation), and are easily comforted by their caregivers. Anxious-avoidant infants show little overt distress (despite physiological indications of distress) when separated and fail to seek—or even actively avoid—comfort from their parents upon reunion. Anxious-ambivalent or -resistant infants show high levels of distress when separated and simultaneously display approach behavior but resistance to comfort upon reunion. Disorganized infants (Main & Solomon, 1986) fail to show a coherent strategy for seeking proximity or comfort and may show anomalous or disoriented behaviors upon reunion (e.g., fearful or freezing behavior).

During middle childhood, attachment typically is assessed using a modified version of the Strange Situation (Main & Cassidy, 1988) or the Attachment Q-Set (Posada, Waters, Crowell, & Lay, 1995), which involves characterizing children on the basis of naturally observed secure base behaviors in the home setting. To tap internal working models during childhood, several methods also assess internalized representations of the attachment relationship. These assessments elicit open-ended verbal and behavioral responses through the use of story prompts or drawings (for a review, see Kerns, 2008). Attachment behavior and representations are coded using categorical classification schemes or continuous measures of security.

In adults, the most common assessment method is the Adult Attachment Interview (Main & Goldwyn, 1998), a semi-structured interview probing adults' state of mind regarding attachment with their caregivers. Based on the coherence of adults' narratives about their early attachment-related experiences (Roisman, Padrón, Sroufe, & Egeland, 2002), they are classified into one of four categories that parallel the infant classifications: secure/autonomous, dismissing, preoccupied, and unresolved. Complementing the developmental psychology tradition of assessing adults' state of mind with respect to early attachment experiences, social and personality psychologists have extended attachment theory to conceptualize romantic bonds in adolescence and adulthood. This perspective presumes that romantic relationships serve attachment functions parallel to those of the parent–child bond (Hazan & Shaver, 1987; for a review, see Mikulincer & Shaver, 2007). Social-personality assessments of adult attachment style involve self-report questionnaires regarding explicit thoughts and feelings within close adult (often romantic) relationships. Adults are characterized along two dimensions of attachment (in)security (Brennan, Clark, & Shaver, 1998; Hazan & Shaver, 1987; Roisman et al., 2007): attachment avoidance (discomfort with closeness and intimacy; reluctance to rely on others for support) and attachment anxiety (desire for extreme closeness and intimacy but fear of abandonment).

Considerable research has tested the key tenets of attachment theory (for reviews, see Cassidy & Shaver, 2008; Roisman & Groh, 2011). There is consistent evidence that parental sensitivity is associated, albeit modestly, with infant attachment security (De Wolff & van IJzendoorn, 1997) although distinct parenting correlates of specific types of insecure attachment have not been clearly established (Roisman & Groh, 2011). Meta-analytic evidence also supports the intergenerational transmission of attachment (van IJzendoorn, 1995) as well as a modest but significant degree of continuity in security from infancy through adulthood (Fraley, 2002).

Documenting the enduring effects of attachment, an impressive corpus of research links security of early

attachment, attachment representations, and adult attachment with a range of indicators of well-being, including self-reliance and self-image, emotion understanding and regulation, personality, and competence within peer and romantic relationships (for reviews, see Roisman & Groh, 2011; Thompson, 2008; Weinfield et al., 2008). Despite this support, the magnitude of effects often lies in the small to moderate range. Also of note, despite their presumed common theoretical origins, developmental and social-psychological assessments of adult attachment share little variance and predict somewhat distinct aspects of functioning within adult relationships (Roisman et al., 2007), suggesting they tap different aspects of attachment.

Application to Psychopathology. There is consistent (although sometimes modest and qualified) support for many of the central tenets of attachment theory with regard to its role in normative development and its contribution to individual differences in competence. Reflecting the generative nature of attachment theory, insecure attachment also has been implicated as a key contributor to psychopathology (for reviews, see Cicchetti et al., 1995; Davila, Ramsay, Stroud, & Steinberg, 2005; DeKlyen & Greenberg, 2008; Kobak et al., 2006). Collectively, these conceptualizations are based on the notion that early secure attachment arising from warm and sensitive caregiving lays the foundation for effective emotion regulation, healthy relationships, and positive working models of the self and others, which foster optimal long-term mental health. In contrast, it is theorized that early insecure attachment arising from unpredictable or rejecting caregiving undermines the formation of interpersonal competence and relationships, generates maladaptive working models of the self and others, and heightens risk for psychopathology.

Reflecting the principle of multifinality, these perspectives incorporate pathways between attachment insecurity and multiple forms of psychopathology. Reflecting the principle of equifinality, these perspectives implicate diverse avenues through which insecure attachment may foster similar outcomes. Proposed mediating pathways include (1) maladaptive internal working models incorporating views of the self as unworthy and ineffective as well as negative expectations of relationships (e.g., lack of support, hostility); (2) ineffective emotion regulation and poor coping skills; (3) cognitive biases (e.g., maladaptive interpretations, attributions, and expectancies); (4) inadequate internalization of social norms; (5) poor modulation of biological stress responses; (6) ineffective behavioral self-regulation (e.g., poor self-control and reciprocity); and (7) a negative social orientation (for reviews, see Brumariu & Kerns, 2010; Davila et al., 2005; DeKleyen & Greenberg, 2008; Weinfield et al., 2008).

In the next few sections, we present some specific representative attachment-based theories of psychopathology and we discuss the status of empirical evidence. Of note, many other theories consider attachment as a central construct. Some of those that implicate attachment within the context of integrative models are discussed in a later section. Overall, an extensive research base supports the proposed association between insecure attachment and multiple forms of psychopathology, with more limited evidence implicating a prospective contribution of insecure attachment to future psychopathology. Many comprehensive summaries of this research are available (Brumariu & Kerns, 2010; Davila et al., 2005; DeKlyen & Greenberg, 2008; Kobak et al., 2006); thus, we present a brief summary of results from recent qualitative and quantitative reviews.

Depression and Anxiety From the seminal work of Bowlby (1973, 1980) to contemporary perspectives (Brumariu & Kerns, 2010; Cassidy, 1995; Cummings & Cicchetti, 1990), attachment theory has been integral to many theories of anxiety and depression. According to Bowlby (1973), family environments that elicit concerns about rejection or abandonment or about the caregivers' or child's well-being prompt insecurity about caregiver availability along with heightened fear and vigilance. These concerns create a vulnerability to anxiety, particularly in the face of subsequent separation or challenge. Bowlby (1980) further asserted that uncontrollable and prolonged caregiver loss—whether symbolic or actual—conveys a sense of hopelessness and failure and invokes an internal working model of the self as unlovable and incompetent and of others as unloving. This working model creates a vulnerability to depression, particularly in the face of subsequent loss or disappointment. Building on these ideas, several contemporary models suggest that insecure attachment constitutes a significant risk factor for internalizing psychopathology. These theories integrate key aspects of Bowlby's original conceptualization while also refining and elaborating on pathways linking insecure attachment with anxiety and depression. Moreover, many of these models attempt to explain the contribution of specific subtypes of insecure attachment to anxiety versus depression, or even to subtypes of anxiety.

According to one model proposed by Sroufe and colleagues (Sroufe, 2003; Weinfield et al., 2008), children with an anxious-ambivalent attachment, who have pervasive concerns about caregiver availability, will be challenged by novel and complex social situations and consequently

will be prone to anxiety. Manassis (2011) speculated that each type of insecure attachment will heighten vulnerability to different types of anxiety. Specifically, children with an anxious-ambivalent attachment would show reduced exploratory behaviors and would be preoccupied with obtaining the caregiver's attention and comfort, thereby promoting separation anxiety. Children with an anxious-avoidant attachment would show heightened fear of rejection and avoid social contact, thereby promoting social phobia; alternatively, their restricted expression of negative emotions could trigger the indirect expression of distress through somatic complaints. Children with a disorganized attachment would be excessively concerned about their caregiver's well-being, potentially leading to separation anxiety and school phobia. Cassidy (1995) proposed that insecure attachment also can serve as a developmental antecedent of generalized anxiety disorder due to emergence of a cognitive style centered on chronic vigilance and ineffective responses to threat (see also Weinfield et al., 2008).

Presenting an attachment-based model of depression, Cummings and Cicchetti (1990) proposed that insecure attachment undermines children's self-esteem, felt security, coping resources, and confidence in the availability of others, thereby promoting long-term risk for depression. This model focuses in particular on the intergenerational transmission of depression, wherein the offspring of depressed parents experience high levels of caregiver psychological unavailability, thus heightening risk for the development of early insecurity, negative working models of self and others, and later disorder. Drawing from Bowlby's ideas, Egeland and Carlson (2004; see also Weinfield et al., 2008) articulated different pathways through which certain types of insecure attachment would lead to depression. Specifically, they suggested that (1) children with an anxious-ambivalent attachment, who feel unable to fulfill their caregivers' demands, develop a sense of helplessness; (2) children with an anxious-avoidant attachment, who perceive themselves as unlovable and inadequate and perceive others as hostile and unsupportive, develop a sense of alienation and hopelessness; and (3) children with a disorganized attachment, who feel overwhelmed by challenge, develop a low sense of self-efficacy. Depression represents the final common pathway of helplessness, hopelessness, and low self-efficacy. Several other theorists have proposed attachment-based models of depression, hypothesizing that insecure attachment confers vulnerability through the development of negative views of self and the social world, ineffective affect regulation and coping, and heightened generation of, or reactivity to, stress within close relationships (e.g., Cole-Detke & Kobak, 1996; Hammen et al., 1995).

Brumariu and Kerns (2010) provide speculative models of differentiated processes through which insecure attachment may contribute to both anxiety and depression. According to the first model, insecure attachment interacts with overcontrolling parenting to predict heightened threat sensitivity, difficulties in emotional understanding and expression, avoidance coping, and low self-efficacy, which heighten vulnerability to anxiety in the face of anticipated threat and in interaction with parental anxiety and temperamental vulnerability (high negative affect, high behavioral inhibition). According to the second model, insecure attachment interacts with rejecting parenting to predict a depressogenic cognitive style, difficulties in emotional understanding and expression, ruminative coping, and low self-worth, which heighten vulnerability to depression in the face of experienced disappointment or loss and in interaction with parental depression and temperament vulnerability.

In a recent narrative review of research on attachment and internalizing symptoms, Brumariu and Kerns (2010) concluded that attachment insecurity is consistently associated with anxiety and depressive symptoms, with stronger associations in preadolescence/adolescence than in earlier childhood. However, they noted the scarcity of prospective longitudinal research, particularly studies that examine changes in internalizing symptoms over time. Effect sizes across studies ranged from small to large, with effects stronger for studies that used questionnaire rather than observational or representational assessments of attachment and significant variability within and across studies depending on the specific comparisons (e.g., general insecurity vs. specific subtypes), informants, or age of symptom assessment. Although a useful preliminary summary of the state of the field, a more definitive quantitative estimate was provided by a recent meta-analysis that incorporated only studies using state-of-the-art observational measures of attachment during early childhood (Groh, Roisman, van IJzendoorn, Bakermans-Kranenburg, & Fearon, 2012). This analysis yielded a significant, albeit small, effect size for the association between attachment and internalizing symptoms, which was not significantly moderated by age of symptom assessment, child gender, economic risk or clinical status of the sample, type of attachment measure, or type of internalizing symptom measure.

Externalizing Psychopathology Attachment theory also has been invoked to explain the emergence of externalizing psychopathology. According to Bowlby (1973), prolonged

caregiver separation, rejection, or the threat of abandonment invoke intense anger in children. Originally directed toward the attachment figure, children may learn to redirect anger toward other targets, resulting in hostile and aggressive behavior. Building on these ideas, Sroufe (2003; Weinfield et al., 2008) proposed that both avoidant and ambivalent attachment would promote risk but for different reasons and with different manifestations. Whereas children with an avoidant attachment may develop aggressive and antisocial behavior (e.g., bullying, blaming, insensitivity) in response to anger stemming from rejection by their caregiver and resulting alienation and lack of social trust, children with an ambivalent attachment may develop behavior problems (e.g., impulsivity, restlessness) as a result of overstimulation and poor self-regulation. Disorganized children also are viewed as at risk for anger and aggression due to their struggles over attachment to a frightened or frightening caregiver (Weinfield et al., 2008).

Greenberg and colleagues (1993; Dyklen & Greenberg, 2008) elaborated on four specific pathways through which insecure attachment can heighten risk for disruptive behavior disorders. First, insecurely attached children may develop working models of relationships characterized by anger and mistrust, resulting in cognitive biases (e.g., hostile attributions) that set the stage for reactive forms of aggression. Second, insecure attachment may promote maladaptive regulatory behaviors (e.g., whining, noncompliance) aimed at seeking attention and proximity to the caregiver, which later consolidate into general patterns of externalizing behavior. Children with disorganized attachment, in particular, may aim to take control of the parent–child relationship in an effort to create a more coherent and predictable environment, resulting in dominating social behaviors. Third, insecurity may undermine effective emotion regulation processes, such that avoidant children minimize, and ambivalent children exaggerate, negative affect, both of which may cause problems dealing with later stress. Fourth, insecurely attached children may develop a resistant social orientation, making them less amenable to moral directives and social norms that would inhibit deviant behavior. Acknowledging the complexity of the proposed processes, however, these theorists note the improbability that insecurity exerts main effects on behavior problems, instead taking a multiple pathways perspective that considers how attachment security likely interacts with other risk and protective factors concurrently and later in development to determine behavioral trajectories.

Two recent meta-analyses examined the link between attachment and externalizing psychopathology. One (Fearon, Bakermans-Kranenburg, van IJzendoorn, Lapsley, & Roisman, 2010) yielded a medium effect for the link between general attachment insecurity and externalizing symptoms. Moreover, the predictive significance of attachment insecurity remained constant across the age of symptom assessment but was stronger for boys and for clinical samples. The other (Hoeve et al., 2012) yielded a small-to-moderate effect for the link between insecure attachment and delinquency. However, this effect was moderated by a number of factors, including age (larger for younger than older children), attachment figure (larger for mother–child than father–child attachment), and match between sex of the parent and child (larger for same-sex than cross-sex pairs). Discrepancies across these two reviews (e.g., absence vs. presence of a moderating effect of age) may be due in part to a focus on externalizing symptoms more broadly in the former study versus delinquency specifically in the latter study as well as the inclusion of studies using a broader array of attachment measures in the latter than former study. Of note, Groh et al. (2012) found that the meta-analytic effect for externalizing symptoms in the Fearon et al. (2010) study was significantly larger than their effect for internalizing symptoms.

Eating Pathology Attachment also plays a central role in several theories of eating disorders. Dating back to the early writings of Bruch (1973), integral to these theories is the idea that eating pathology emerges in the context of poor self-individuation from attachment figures, anxiety about the availability of attachment figures, and efforts to ensure proximity to caregivers. Demands for heightened autonomy from caregivers during adolescence are believed to trigger extreme confusion and anxiety, as insecurely attached youth struggle to develop a sense of self as competent and self-sufficient when facing psychological separation (i.e., individuation) from their caregivers. Armstrong and Roth (1989) proposed that eating disorder symptoms serve to regulate negative affect and anxiety about this separation and to maintain connectedness to caregivers; as such, symptoms provide insecurely attached youth with a sense of control in the face of perceived helplessness. The assumption is that insecurely attached youth not only have excessive concerns about separation but they also lack effective emotion regulation skills necessary to cope with the challenges of adolescence. Thus, disordered eating may reflect an attempt to control one's world by directing attention away from attachment toward more attainable and less anxiety-provoking goals (Cole-Detke & Kobak, 1996). O'Kearney (1996) suggested that symptoms of anorexia and bulimia function to regulate proximity to

caregivers. For youth with a dismissing (avoidant) attachment, symptoms cause an altered physical appearance that diverts attention away from distressing aspects of the attachment relationship. For youth with a preoccupied (ambivalent) attachment, a focus on appearance is thought to reflect hypervigilance to the judgments of others.

Most of the research examining the association between insecure attachment and eating disorders involves adult samples (for a review, see Davila et al., 2005). Overall, this research suggests high rates of concurrent insecure attachment in women with eating disorders. Attempts to identify links between specific subtypes of attachment and specific types of eating disorders have not yielded a consistent pattern, with some studies suggesting strong links with preoccupied attachment and others with dismissing attachment. These discrepancies may be due in part to different patterns of comorbidity within the eating disorder groups (Davila et al., 2005). Unfortunately, much of this research relies on non-standard measures of attachment; moreover, prospective research has not yet investigated whether early attachment predicts long-term risk for eating disorders, making it difficult to draw definitive conclusions about its etiological status.

General Parenting and Family Theories

Theoretical Underpinnings. Beyond the level of the parent–child attachment bond, parenting and family theories focus on three primary types of influence. One set of theories emphasizes parenting practices and styles, including parents' behavior toward children and the emotional climate of the parent–child relationship. Another set of theories focuses on parental modeling, reinforcement, and instruction, which can entail both negative influences (e.g., parental modeling of aggressive behavior) and positive influences (e.g., parental coaching in adaptive coping strategies). A third, family systems theory, expands beyond the parent–child dyad to include other subsystems within families such as interparental and sibling relationships.

Parenting Practices and Styles Parenting theorists distinguish between parenting practices (what parents do) and styles (how they do it). Several theoretical perspectives draw similar conclusions about the major dimensions underlying parenting practices and styles. Early theories emphasized the importance of acceptance versus rejection and dominance versus submission (Symonds, 1939); warmth versus hostility and detachment versus involvement (Baldwin, 1955); warmth and permissiveness versus strictness (Sears et al., 1957); love versus hostility and autonomy versus control (Schaefer, 1959); and warmth versus hostility and restrictiveness versus permissiveness (Becker, 1964). These theories share a framework focusing on dual dimensions of parenting: emotional (captured in the constructs of acceptance and warmth vs. hostility and rejection) and behavioral (captured in the constructs of involvement and autonomy vs. restrictiveness and control). Contemporary theories view these as orthogonal dimensions of parenting.

Baumrind's (1967) well-known conceptualization incorporated these two key dimensions of parenting into a typology of three styles: authoritarian, authoritative, and permissive. Authoritarian parents are highly controlling, giving directives for their children to follow without an opportunity to provide input or make independent choices. Permissive parents are warm and affectionate but highly lenient, giving children a great deal of freedom to do as they please. Authoritative parents share a mixture of these characteristics; they are affectionate but also provide clear rules along with explanations for why children should follow them. Compared to children whose parents are authoritarian or permissive, children of authoritative parents show the highest levels of subsequent social competence and academic achievement and the fewest behavior problems (Baumrind, 1971). Lewis (1981) reinterpreted Baumrind's work to emphasize that reciprocal communication and children's empowerment to negotiate rules in authoritative families, rather than high control, promotes children's autonomy and social competence.

Building on Baumrind's perspective, Maccoby and Martin (1983) conceptualized parenting in terms of a two-by-two matrix reflecting high versus low levels of demandingness (control, supervision) and responsiveness (warmth, acceptance). Authoritarian parents were high on demandingness but low on responsiveness, and authoritative parents were high on both demandingness and responsiveness. However, Maccoby and Martin differentiated permissive parents into indulgent parents, who were low on demandingness but high on responsiveness, and neglecting parents, who were low on both demandingness and responsiveness. Following this distinction, Baumrind (1991) later incorporated into her own framework a rejecting-neglecting style in which parents were low on both demandingness and responsiveness. Baumrind (1991) also differentiated the nature of demandingness such that authoritative parents use firm control but are not highly restrictive, whereas authoritarian parents use firm control but are also highly restrictive.

Baumrind's differentiation of restrictiveness from firm control foreshadowed what has become an important distinction between psychological and behavioral control

(Barber, 1996). Psychological control involves manipulation and intrusion into children's emotional and cognitive world through invalidating children's feelings and pressuring them to think in particular ways. These psychologically controlling behaviors are associated with worse adolescent adjustment, such as more delinquency, more depression, and poorer academic achievement (Barber, 2002). Behavioral control involves parents' attempts to regulate children's behavior through monitoring, guidance, and supervision; this regulation can be accomplished through parents' behaviors (e.g., setting rules such as curfew times) and parents' knowledge about adolescents' whereabouts, companions, and how they spend their time, which can be a function of parents' own efforts as well as adolescents' willingness to disclose information to their parents (Stattin & Kerr, 2000). In contrast to psychological control, behavioral control generally is associated with better adolescent psychological and behavioral adjustment (Pettit, Laird, Bates, Dodge, & Criss, 2001).

In part in response to inconsistent findings regarding how specific parenting practices are related to children's adjustment, another set of theories emphasizes parenting style as a context that moderates the link between specific parenting practices and children's adjustment. Darling and Steinberg (1993) distinguished three aspects of parenting: parents' goals for their children's socialization, parenting practices, and the emotional climate in which parents socialize their children (i.e., style). They argued that parenting style moderates the effectiveness of specific parenting practices and modifies children's openness to being socialized. These three aspects of parenting comprise a model with five components. Parenting goals and values (component 1) influence both parenting style (component 2) and parenting practices (component 3), which directly affect child outcomes (component 4); however, the relation between parenting practices and child outcomes is moderated by parenting style and children's willingness to be socialized (component 5), which also is affected by parenting style.

Several other contemporary models also introduce the role of parents' and children's emotions as well as children's subjective perceptions of parenting as key mediators of parenting effects. Davies and Cummings (1994) summarized research on two broad categories of parenting problems—parental rejection (including negative emotions) and poor child behavior management—in the context of their emotional security hypothesis. According to this framework, children's emotional security mediates the link between parenting and children's adjustment. Parents' negative emotions, including intrusiveness, withdrawal, and rejection, contribute to children's anger, dysphoria, social withdrawal, noncompliance, and externalizing problems. In terms of poor child behavior management, Davies and Cummings described two problematic parenting patterns. The first is characterized by lax supervision and discipline, whereas the second is characterized by harsh discipline. Both are predictive of children's externalizing and internalizing problems. Davies and Cummings interpret these links in the context of an emotional security hypothesis, which posits that when parents are unavailable or unpredictable, children's sense of emotional security and ability to regulate their own emotions are compromised. Most of their research focuses on children's emotional insecurity in the face of marital conflict, but the proposed mechanisms share features of attachment theory and other prominent parenting theories, which propose that children's interpretation of parents' behavior is a key factor in the link between parenting and children's adjustment.

In a similar vein, Rohner's (2004) parental acceptance–rejection theory posits that children's interpretation of their parents' behavior as indicating acceptance or rejection determines its effects on development. Meta-analyses and systematic reviews of data from many countries support this proposition (e.g., Khaleque & Rohner, 2002). In one investigation, Rohner, Bourque, and Elordi (1996) found children's perceptions of the harshness and justness of their parents' physical punishment did not have direct effects on their psychological adjustment; instead, these effects were fully mediated by children's perceptions of their parents' acceptance and rejection. Similarly, Rohner, Kean, and Cournoyer (1991) found that parents' use of physical discipline negatively affects children's adjustment in part through its effect on children's perception of being rejected. Thus, the effect of a particular parenting behavior may depend on the context in which it is employed and the meaning it delivers for the parent and child.

Dix (1991) describes three types of processes in an emotion-focused model of parenting. Activation involves when emotion is experienced, what emotion is experienced, and how strongly it is experienced. Engagement orients people to events in a way that is consistent with the emotion and affects their cognition about the event, physiological state, behavioral orientation, expression of emotion, and motivation. Regulation involves processes that help people understand and control their emotions, including how emotions are expressed (e.g., by augmenting positive emotions or inhibiting negative emotions). Emotions are activated in parent–child interactions because these interactions are important to parents. Parents often

have particular short-term (e.g., get the child to school on time) and long-term (e.g., promote honesty, responsibility, and empathy) goals in parent–child interactions; emotions often hinge on whether parents' goals in a particular interaction are promoted or thwarted. When parents and children have compatible concerns and behaviors, emotion generally will be positive; when they have divergent concerns and behaviors, emotion often becomes negative. Parents can manage this divergence with a variety of strategies. They can use cooperative strategies such as negotiating and reasoning. Alternatively, parents can use forceful strategies by imposing their will; because this approach does not reconcile children's and parents' wants, children are likely to resist more and, therefore, these strategies may undermine future cooperation and support in parent–child relationships. Finally, parents can use empathic strategies by accommodating to the child's desires.

The strength of a given emotion depends on parents' perceptions of whether the event that induced the emotion is important, stable, and controllable. Too little emotion can lead to parenting that is disengaged or unresponsive, but too much emotion can lead to parenting that is too harsh or intrusive, both of which characterize distressed parents. Emotion regulation is important for parents because it ensures that parents do not display counterproductive emotions (e.g., parents may suppress expressions of their own fear to avoid making their young children fearful) or that are poorly matched to a particular parenting situation (e.g., if parents bring home anger from an interaction at work and take it out on the child). Dix (1991) argued that parenting will be most effective when children's concerns activate stronger emotion than parents' concerns because parents will then act empathically in the child's interests even if it is not personally convenient or easy to do so.

Parental Modeling, Reinforcement, and Instruction Social learning models focus on exposure to healthy versus pathogenic learning environments within the family (for a review, see Davies & Sturge-Apple, 2014). Learning can occur through observational (vicarious), enactive (reinforcement), and instructional processes. In observational learning, children adopt cognitive, emotional, and behavioral repertoires through imitation and the internalization of schemas or scripts. In risky family environments, parents may express unhealthy cognitive biases (e.g., negative attributions, hypervigilance to threat), show high levels of emotional distress (e.g., extreme anxiety), and engage in maladaptive behaviors (e.g., poor coping, aggression) due to their own psychopathology or other personality characteristics, thereby transmitting unhealthy patterns to their offspring. In enactive learning, parents may manage children's behavior using reinforcement contingencies that purposefully or inadvertently reinforce either salutary or deviant behaviors. Inept parenting behaviors (e.g., lax or inconsistent discipline; poor communication of expectations) can have the effect of failing to reward prosocial behaviors and failing to punish antisocial behaviors, thereby conveying confusing messages about appropriate behavior. Unfortunately, parenting behaviors aimed at protecting children (e.g., limiting contact with anxiety-inducing situations; permitting or encouraging avoidance) can serve to negatively reinforce maladaptive emotions and behavior. Parents also provide direct instruction regarding appropriate modes of functioning, encouraging children to cope with emotions and stress in ways that foster either healthy or unhealthy patterns (Abaied & Rudolph, 2010). Collectively, these learning processes result in the intergenerational transfer of unhealthy cognitive, emotional, and behavioral styles that heighten risk for psychopathology.

Family Systems Theory Family systems theory posits that the entire family, rather than just individual dyads within families, should be the unit of analysis when trying to understand links between family functioning and children's development (Davies & Cicchetti, 2004). Dyadic parent–child, interparental, and sibling relationships are all important, but family systems theory advocates an approach to families that goes beyond individual dyads. Key concepts in family systems theory include holism, interpersonal boundaries, and embeddedness (Cox & Paley, 1997).

The concept of *holism* encompasses understanding families as consisting of interdependent parts (Davies & Sturge-Apple, 2014). Families include subsystems of interconnected relationships (e.g., mother-child, father-child, brother-sister, mother-father, etc.) that, as a unit, represent more than the additive sum of these subsystems (Cox & Paley, 1997). Functioning within one relationship, or subsystem, can affect all other individuals and relationships, and relationships are bidirectional. Within the family system, individuals can have direct effects on one another or can have indirect effects when dynamics from one relationship influence dynamics in another relationship, such as when interparental conflict spills over into hostile parent–child interactions (Schoppe-Sullivan, Schermerhorn, & Cummings, 2007). Because of this interdependency, disturbances in any subsystem can have implications for other subsystems.

The concept of *interpersonal boundaries* also plays a key role in family systems theory. The exchange of resources

and information within families has been described in relation to four patterns of boundaries: cohesive, disengaged, enmeshed, and triangulated (Davies & Sturge-Apple, 2014). Cohesive families have flexible and well-defined boundaries that give children access to resources such as warmth and guidance yet also enable children to retain autonomy and individuality. In cohesive families, conflict and distress tend not to spill over from one relationship subsystem to others and are typically mild and well managed. Children in cohesive families generally have better developmental outcomes than do children in other types of families. Disengaged families have rigid and inflexible boundaries that prevent children from gaining access across family subsystems to resources such as support and protection (Davies & Sturge-Apple, 2014). Consequently, individuals in disengaged families often feel emotionally detached and alienated. Children in disengaged families are at risk for developing psychopathology characterized by externalizing problems, social withdrawal, and interpersonal disregard (Jacobvitz, Hazen, Curran, & Hitchens, 2004). Enmeshed families have weak boundaries in which children lack autonomy and are exposed to discord in multiple family subsystems (Davies & Sturge-Apple, 2014). For example, in enmeshed families, children may not be shielded from marital conflict, and parents may use psychological control that intrudes on adolescents' ability to gain age-appropriate independence from the family. Children in enmeshed families are at risk for anxiety, other internalizing problems, and interpersonal dependency (Jacobvitz et al., 2004). Triangulated families share characteristics of both disengaged and enmeshed families as reflected in defensive alliances between some family members who are pitted against others from whom they are disengaged. Children who form coalitions with a parent may take on developmentally inappropriate roles as a confidante or caregiver, placing them at psychological risk (Johnson, 2010). Sometimes, children's psychological symptoms themselves serve a function within the family of bringing other family members into an alliance against the child (Davies & Sturge-Apple, 2014).

Families are embedded in the larger world, and this larger context affects what occurs within families. Cultural, social, and economic events can have a tremendous effect on the nature of families and interactions among family members (Bronfenbrenner, 1977). Ecological models are clear in documenting that understanding children's development in family systems is not independent of what is happening outside the family. For example, Elder's (1974) classic study of children of the Great Depression demonstrated that children's developmental outcomes were contingent not only on family processes but also on economic strain resulting from the Depression as well as children's age at the time, with individuals who were adolescents during the Depression faring more favorably than those who were children.

Family systems theory has the potential to contribute to an understanding of children's adjustment above and beyond parenting theories. As described previously, several parenting theories emphasize the importance of parental warmth and affection in fostering positive developmental outcomes. Family systems theory contextualizes this idea by emphasizing that parental warmth might have different meanings in the context of different types of families. For example, parental warmth may be a manifestation of healthy family functioning, an attempt by a parent to compensate for other forms of adversity in the family, or a coalition-building attempt by one parent against the other (Davies & Cicchetti, 2004).

Even within family systems theory, the majority of attention is devoted to interparental and parent–child subsystems rather than to sibling subsystems. Nevertheless, sibling relationships are an important interpersonal context and can play a meaningful role in children's development. In the United States, approximately 80 percent of children have at least one sibling (Livingston, 2011). On average, children spend more time with their siblings than with their parents (McHale & Crouter, 1996). Chronic and physical conflict between siblings is related to children's internalizing (Milevsky & Levitt, 2005) as well as externalizing problems (Ensor, Marks, Jacobs, & Hughes, 2010). In contrast warmth and cohesion between siblings is related to fewer externalizing problems (Branje, Van Lieshout, Van Aken, & Haselager, 2004) and more positive psychological functioning (Stocker, 1994).

Expressed emotion (EE) theory provides another lens through which to understand links between family functioning and psychopathology (Brown, Birley, & Wing, 1972). Originally developed to explain the course of severe mental illness such as schizophrenia, this theory has been extended to understand the development of other disorders, including mood and eating disorders (Butzlaff & Hooley, 1998). The assumption of EE theory is that emotions operate as a salient socializing force within the family; a particular emphasis is placed on the dimensions of hostility, criticism, and emotional over-involvement. Hostility and criticism often involve either blaming an individual for problems in the family or blaming a family member for not controlling his or her disorder. Emotional over-involvement often involves family members blaming themselves for another family member's disorder. In a

meta-analysis of 27 studies, EE was a significant predictor of relapse in schizophrenia, mood disorders, and eating disorders (Butzlaff & Hooley, 1998).

Integrative Parenting/Family Model Integrating diverse parenting and family theories of psychopathology, Davies and Sturge-Apple (2014) proposed a comprehensive, developmental family risk model. In their model, family dynamics include both family risk factors (quality of relationships within the parent–child, interparental, and child-sibling subsystems) and systemic organizing parameters (interdependency, holism, and boundaries). The systemic organizing parameters describe how the subsystems relate to one another, such as interdependency related to spillover of conflict from the interparental relationship to parent–child relationship and whether there are well-defined boundaries between family members. Family risk factors and systemic parameters are thought to influence child psychopathology through cascade mechanisms (interpersonal, neurobiological, neuropsychological, and stage-salient tasks). Bidirectional associations between family dynamics and child adjustment trajectories operate via family risk mechanisms (child attachment insecurity, child defensive reactivity, and child affiliative styles) and can be moderated by regulatory conditions (parent characteristics, ecological factors, and child attributes).

Developmental Significance and Change. Different aspects of parenting and family relationships are salient at different stages of development (for a review, see Grusec & Davidov, 2007). During infancy, responsiveness and sensitivity are essential to foster healthy parent–child attachment relationships. During early childhood, children's social and emotional development is encouraged by parents' scaffolding of children's experiences in a way that promotes their self-regulation and emotion socialization as well as their development of executive function skills. During middle childhood, behavioral control becomes more salient as parents attempt to effectively prevent and respond to misbehavior. Normative development is promoted via parents' setting and enforcing appropriate limits, proactive behavioral management, and provision of warmth and acceptance. In adolescence, it is important for parents to continue providing warmth and acceptance and appropriate behavioral regulation. At the same time, promoting autonomy and independence are increasingly important. During adolescence, distal monitoring and psychological control become more salient as adolescents spend more time outside the direct control of parents and in the presence of their peers. The transition through puberty also may significantly transform and challenge family relationships as parents and youth attribute different meaning to advancing maturation, with parents focusing on increasing responsibility and risk, and youth focusing on increasing privilege and autonomy. Negotiating the push and pull of parent–child relationships as adolescents seek autonomy yet retain connections with the family can serve as a significant stressor to the family system.

Early theory and research focused largely on how parents affect children's development during each of these developmental stages. However, the seminal writings of Bell (1968) and Scarr and McCartney (1983) spurred a new scientific tradition focused on understanding transactions between children and their parents. These reciprocal effects can unfold moment by moment (Bell, 1968) or over longer periods of time (Sameroff, 1975). Sameroff's (1975) model asserts that children and their parents mutually affect one another when children elicit particular types of responses from their parents and when parents' behavior induces children to behave in particular ways. Parent effects can be accounted for by mechanisms discussed earlier, such as parenting practices and styles, learning processes, and family dynamics. Child effects can be accounted for by mechanisms such as temperamental eliciting of particular parenting behaviors and rGE effects. As children develop and are given more opportunities to act independently on the environment, rGE effects move from being driven primarily by passive processes to more evocative and active ones (Scarr & McCartney, 1983). Although some research suggests the primacy of child or parent effects, there is more empirical support for reciprocal relations (see Special Section of *Journal of Abnormal Child Psychology*, 2008).

Along with transformations within parent–child relationships, entire families are dynamic. Some family changes involve normative transitions as children develop (and therefore require change within the family to accommodate their new capabilities and needs) and as parents develop (for example, once they have progressed beyond the transition to parenthood and have moved into a more established parenting role). Sources of change also can include events inside families such as the birth of a new baby, parental divorce, or illness or death of a family member. Finally, changes can be instigated by outside forces, such as a parent's job loss or a child's academic difficulties or successes.

Normative development often is distinguished from non-normative development by virtue of disruptions in family relationships. For example, parent–child relationships that are physically, emotionally, or sexually abusive are non-normative and confer risk for negative developmental outcomes. Likewise, family experiences that

are off-time by virtue of their occurrence either before or after they would be expected normatively also confer developmental risk. For example, teen parenthood often is associated with academic, psychological, and behavioral difficulties in both the teen parents and their offspring.

Application to Psychopathology. Parenting and family theories offer several explanations regarding why problems in parent–child relationships predict certain types of psychopathology. Reflecting *multifinality*, theories delineate ways in which the major dimensions of parenting affect multiple forms of psychopathology. Reflecting *equifinality*, theories suggest that different aspects of parenting and family relationships ultimately may be related to similar forms of psychopathology via several mediators (e.g., children's emotion regulation, emotional insecurity, perceptions of their parents' rejection). In the next few sections, we present some representative parenting and family systems theories as related to psychopathology.

Depression Driven by robust evidence for the intergenerational transmission of depression, many theories of youth depression consider the idea that depressed parents contribute not only genetic and neurobiological liability but also socialization contexts conducive to the development of depression in offspring. Specifically, several theories (Abaied & Rudolph, 2014; Goodman & Tully, 2008; Hammen, Rudolph, & Abaied, 2014) propose a transmission process wherein maternal depression and its cognitive and emotional sequelae disrupt parenting behavior and parent–child relationships, creating stressful contexts and functional deficits that predispose youth to depression. These perspectives collectively focus on the contribution of multiple parenting dimensions thought to characterize both depressed parents and the parents of depressed youth: (1) high levels of hostility, rejection, and criticism; (2) low levels of support, warmth, and positive affect; (3) high levels of psychological control and intrusiveness; and (4) maladaptive socialization of emotion and coping (e.g., frequent expression of negative emotion or punitive responses to children's emotional displays; encouragement for children to avoid stress and negative emotions). Exposure to these parenting environments (among other early adversities) is thought to impair biological, emotional, cognitive, and interpersonal development in ways that leave youth vulnerable to depression (Hammen et al., 2014). Moreover, transactional processes may emerge in which depressive symptoms color perceptions of the parent–child relationship and induce discomfort and stress in relationships, thereby disrupting future parenting (Abaied & Rudolph, 2014).

Sheeber and colleagues (2001) proposed a model that incorporates similar elements but also considers conditioning within the parent–child relationship, suggesting four pathways to depression. First, the presence of stress and absence of support in parent–adolescent relationships is a risk factor for the development of depression. Second, parents may inadvertently condition their adolescents to exhibit depressive symptoms via negative and positive reinforcement (e.g., reducing parent-to-child aggression or increasing supportiveness in the face of adolescents' depressive behaviors). Third, depressive cognitive styles and ineffective problem-solving skills in children may mediate the relation between problematic parenting and adolescents' depressive symptoms. Finally, parents of depressed adolescents are less skilled at teaching their adolescents to regulate negative affect in constructive ways. In concert, these mechanisms contribute to links between problematic parenting and the development of depression.

Supporting these theories, prospective research using multiple methods (e.g., self- and parent reports, interviews, observations) implicates parenting disruptions as consistent predictors of youth depression and, less frequently, as mediators between maternal and youth depression (for reviews, see Abaied & Rudolph, 2014; Goodman & Tully, 2008; Hammen et al., 2014). At a macro-level (reflecting general parenting practices and style), depressed mothers have particular difficulty with the emotional aspects of parenting, showing less warmth, positive affect, and supportiveness along with more criticism, hostility, and guilt induction (for a meta-analysis, see Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Exposure to these contexts, in turn, predicts youth depression, perhaps in part as a process of social contagion as depressed mothers model maladaptive affect and cognition. At a micro-level (reflecting moment-to-moment contingencies), maladaptive conditioning processes occur, wherein coercive parent–child interchanges heighten youths' vulnerability to subsequent depression. Supporting reciprocal-influence models, some research links depressive symptoms to increasingly negative perceptions and stress within parent–child relationships, although this evidence is mixed.

Anxiety Parents can influence the development and maintenance of anxiety in their offspring through several pathways (for a review, see Vasey, Bosmans, & Ollendick, 2014). In one conceptualization, Murray, Creswell, and Cooper (2009) proposed three such pathways: (1) genetic vulnerability; (2) modeling of anxious cognitions and behavior; and (3) socialization efforts that lead children to believe the world is dangerous and they are unable to cope. Theories of anxiety also propose indirect pathways

through which parents convey anxiety-inducing messages about children and the world, with a particular focus on the parenting dimensions of psychological control or intrusiveness, overprotectiveness (e.g., limiting exposure to challenging or fear-provoking stimuli), and rejection-criticism (Creswell, Murray, Stacey, & Cooper, 2011; Davila et al., 2010; Vasey et al., 2014; Whisman & Beach, 2010). These parenting practices and styles are believed to instill anxiety by lowering children's perceptions of control, compromising their feelings of competence and mastery, restricting their sense of autonomy, heightening their threat sensitivity, and interfering with their emotion regulation (Albano, Chorpita, & Barlow, 2003; Vasey et al., 2014; Whisman & Beach, 2010). Anxiety is then maintained through parental reinforcement (e.g., encouraging or allowing avoidance and escape of a phobic stimulus) and accommodation (e.g., participating in compulsive rituals), which result in a failure to habituate to anxiety-inducing stimuli and to acquire age-appropriate coping and social skills (Kraper, Soto, & Carter, 2014; Whisman & Beach, 2010). Although well intentioned, such reinforcement and accommodation can have the unintended effect of supporting and perpetuating anxiety.

Reflecting transactional processes, children with anxious temperaments or early symptoms of anxiety also may elicit protective or critical behavior or encouragement to avoid stressful situations from their parents (Albano et al., 2003; Kraper et al., 2014), and parent and child displays of anxiety may become mutually reinforcing (Davila et al., 2010). Many of these processes are likely exacerbated in the context of parental anxiety, contributing to the intergenerational transmission of disorder (Albano et al., 2003; Davila et al., 2010; Kraper et al., 2014; Vasey et al., 2014).

A recent meta-analysis (McLeod, Wood, & Weisz, 2007) supports a significant, albeit relatively small, linkage between parenting and anxiety, with larger effects for the dimensions of overcontrol and low autonomy-granting relative to parental rejection and lack of warmth. Overall, research suggests that the magnitude of parenting-anxiety associations varies according to several parameters (e.g., age, informant, sample, methodology; Creswell et al., 2011) and is moderated by child temperament (Vasey et al., 2014). Stronger effects emerge when youth rather than parents serve as informants (McLeod et al., 2007), consistent with the emphasis of some theories on mediation of parenting effects by children's subjective perceptions. Of note, much of the evidence on parenting-anxiety linkages comes from cross sectional research, although some recent longitudinal research supports bidirectional associations between parenting and child anxiety (Vasey et al., 2014).

Externalizing Psychopathology Parenting and family relationships play a key role in most theories of externalizing psychopathology. Patterson and colleagues' (Patterson, Capaldi, & Bank, 1991) coercion theory has been particularly influential in efforts to understand the development of aggressive and antisocial behavior. Coercive exchanges are bidirectional processes in which children influence their parents and parents influence their children in an escalating cycle of negative affect and behavior. As a result of these cycles, aversive behaviors in children (e.g., whining, yelling, hitting) are inadvertently reinforced through parental withdrawal of discipline; likewise, parental ineffective discipline is reinforced through children's temporary reduction in aversive behaviors. These coercive patterns are generalized to interactions between children and others in their environments (e.g., peers, teachers) as children learn to use aversive behaviors to attain rewards or avoid unpleasant experiences, resulting in the perpetuation and exacerbation of aggressive and antisocial behavior (Dishion, 2014).

Other social learning models also explain emerging risk for externalizing psychopathology. Children exposed to corporal punishment may observe and imitate parents' use of aggression; indeed, parents' use of corporal punishment is a robust predictor of children's externalizing behavior (for a review, see Gershoff, 2002). Similarly, according to Huesmann and Guerra (1997), children develop normative beliefs about aggression based on experiences within the family. If children experience aggression in parents, they may come to perceive aggression as being an acceptable and legitimate way of handling problems. More generally, parenting styles characterized by high levels of rejection, high levels of psychological control, and low levels of parental warmth may provide models of hostility and aggression as well as insufficient opportunities for children to learn prosocial behavior, creating risk for externalizing behavior (Barber, 1996). Poor monitoring and lack of supervision may allow adolescents to engage in risky environments and behaviors, promoting and maintaining antisocial behavior (Barber, Stolz, & Olsen, 2005).

Beyond the parent–child dyad, a large body of research links disruptions in family systems or subsystems within families to children's externalizing psychopathology. There is some evidence that taking into account the full family system leads to better prediction of children's externalizing psychopathology than does attention to any single component of the family. For example, Ingoldsby, Shaw, and Garcia (2001) found that children's aggression at school was predicted by exposure to distress in more than one family subsystem rather than exposure to distress in just one. Overall, there is considerable theoretical and empirical

work implicating the linkage between family functioning and the development of externalizing psychopathology (for a review, see Davies & Sturge-Apple, 2014). Developmental cascade models capture well how minor problems in self-regulation during infancy can develop into major problems in externalizing psychopathology through a series of maladaptive transactions between parents and children and noxious family environments (Dishion, 2014).

Of course, it is essential to consider transactional processes wherein children with predispositions toward aggression and antisocial behavior elicit adverse parenting and disrupt the family system. Children with irritable temperaments and high levels of negative emotionality may evoke rejection and hostile or inconsistent discipline from parents and may react in more adverse ways to parent socialization efforts (Bates, Schermerhorn, & Goodnight, 2010). Indeed, consistent with theories of rGE correlations, genetically influenced conduct problems are implicated in an evocative child effect on maternal sensitivity (Deater-Deckard, 2009).

Eating Pathology Family systems theory concepts of enmeshment, overprotectiveness, rigidity, and avoidance of conflict/unresolved conflict have played a prominent role in attempts to understand the development of eating pathology (Minuchin, Rosman, & Baker, 1978). In families characterized by these patterns, eating disorders sometimes develop as a way for children to attempt to exert control and boundaries that are not established in other ways within the family (Blinder, Chaitin & Goldstein, 1988). More broadly, control has emerged as a key issue for individuals with eating disorders, who often attempt to exert control over their lives by controlling their food intake (in the case of anorexia) or who feel out of control with respect to food (in the case of bulimia), both of which have been theorized to stem from inappropriate control within the parent–child relationships (Bruch, 1978). Furthermore, as social learning theory would predict, parents model attitudes and behaviors related to food, eating, and weight (Bruch, 1973).

In part, eating pathology may be transmitted from parents to children in ways that do not directly involve the child's eating. For example, when mothers with bulimia are binging and purging, they are more likely to ignore the child or to become irritable and physically violent (Stein & Fairburn, 1989). Thus, equifinality may characterize the development of eating pathology, with both general parenting problems such as authoritarian control or lack of affection as well as eating-specific problems such as modeling unhealthy attitudes about food leading to children's eating pathology.

Directions for Future Research on Parent–Child and Family Theories

With regard to attachment theory, reviews and meta-analyses support a reliable and enduring, albeit modest, effect of insecure attachment on psychopathology, with a particularly strong effect for externalizing behavior. However, future research will need to address several unanswered questions to provide a more nuanced perspective on the role of early attachment in the development of psychopathology.

First, the jury is still out regarding the validity of theoretical predictions regarding the contribution of specific types of attachment to specific types (or subtypes) of disorder. Thus far, despite some evidence for specificity of effects, contradictory evidence and a lack of consensus abound within the field. In their narrative review, Brumariu and Kerns (2010) concluded that ambivalence poses a higher risk for preadolescence/adolescence anxiety and global measures of internalizing symptoms than do other subtypes of attachment (consistent with some theoretical predictions; Sroufe, 2003; Weinfield et al., 2008), and that avoidance was not consistently associated with internalizing symptoms. They also concluded that disorganization was moderately associated with depression. Yet, in their meta-analytic review, Groh and colleagues (2012) found that avoidance but neither resistance nor disorganization significantly predicted internalizing symptoms. There are likely several reasons for these differences, most notably the inclusion of additional studies and the focus on standardized observations of attachment organization in the meta-analysis (vs. the inclusion of self-report and representational measures of attachment during later childhood and adolescence in the narrative review). With regard to externalizing symptoms, Fearon et al. (2010) found a significant effect for disorganization, a small but significant effect for avoidance, and a nonsignificant effect for ambivalence. Disorganization was significantly more strongly associated with externalizing than internalizing symptoms (Groh et al., 2012). Thus, there is not yet a consensus regarding links between specific types of attachment and specific disorders.

Second, adaptations of attachment theory to explain the development of psychopathology often fail to consider the probabilistic nature of the theory's assumptions regarding attachment continuity (Roisman & Groh, 2011). Both theoretical accounts and empirical investigations need to better reflect this aspect of attachment theory by considering characteristics of children or their environments that may account not only for continuity but also for change in attachment organization across development.

Indeed, Bowlby's original conceptualization allows for the possibility that working models can be updated across development based on attachment-relevant experiences, resulting in change over time (Bowlby, 1973; Thompson, 2008). Consistent with this idea, research reveals only moderate stability in attachment organization across the life span (Fraley, 2002). Research therefore needs to consider how changes in the attachment context—either the development of new secure attachments or the loss of previous secure attachments—have the potential to trigger discontinuity between early attachment and subsequent psychopathology.

Third, theory and research need to consider more fully potential individual differences in the contribution of attachment security to psychopathology. Given that attachment theory is a theory about the normative development of, and the emergence of individual differences in, response to threat or challenge, it is logical to conclude that attachment patterns would have a particularly large impact in such contexts. Illustrating this idea, Davila and colleagues (2005) presented an overarching vulnerability-stress model of insecure attachment as a risk factor for psychopathology, suggesting that attachment insecurity can be viewed as a vulnerability or risk within this framework. Consistent with the concept of multifinality, this type of model helps to explain when or for whom attachment insecurity will confer risk for psychopathology. Conceptualized as a stressor, insecurity would trigger psychopathology in youth with predisposing vulnerabilities (e.g., genetic predisposition, temperamental vulnerability). Conceptualized as a vulnerability, insecurity would promote psychopathology in the face of adversity (e.g., normative developmental transitions, life stressors). Similarly, Cummings and Cicchetti (1990) suggest that the contribution of insecure attachment to depression is multidetermined, depending on potentiators (factors that increase the probability of insecure attachment leading to depression) and compensators (factors that decrease the probability of insecure attachment leading to depression) and on the dynamic transactions between children and their environments. Indeed, reviews of empirical support linking insecurity with psychopathology have concluded that evaluating main effects of attachment, particularly in low-risk samples, is likely a futile endeavor as this approach does not appreciate the complexity of attachment theory or its qualified assumptions regarding continuity across development (DeKlyen & Greenberg, 2008).

With regard to more general dimensions of parenting, theory and research consistently implicate a variety of forms of problematic parenting in the development of diverse problematic outcomes. A challenge for future research will be to understand the parameters that shape the contribution of specific forms of parenting to specific forms of psychopathology. Research has begun to move in this direction; for example, appropriate behavioral control primarily has been related to less externalizing behavior, whereas high levels of psychological control and low levels of warmth have been related to more internalizing problems (Gray & Steinberg, 1999). Likewise, in the McLeod et al. (2007) meta-analysis, parental autonomy granting accounted for 18% of the variance in the association between parenting and child anxiety, whereas parental warmth accounted for less than 1% of the variance. Using person-centered rather than variable-centered analyses and considering potential moderators may facilitate progress toward accomplishing this objective because such analyses would be better poised to discover if particular forms of parenting are related to specific child outcomes only in children with certain predispositions, for parents with certain characteristics, or in socioecological contexts with certain features.

Future research also will need to devote more attention to understanding dynamic reciprocal processes between family systems and children's psychopathology. With the advent of sophisticated statistical modeling procedures, research can now move beyond vague disclaimers about a lack of knowledge about the direction of effects between family risk and psychopathology to conduct theoretically guided examinations of transactional effects and pathways of influence. These analyses will capture the dynamic, interdependent processes that are central to contemporary parenting and family theories of psychopathology.

Theories Focused on the Peer Context

There is a long history of research establishing that early disturbances within the peer group forecast proximal as well as long-term risk through adolescence and adulthood (for a review, see Parker, Rubin, Erath, Wojslawowicz, & Buskirk, 2006). Drawing from a developmental psychopathology perspective, several overarching models have been proposed to explain this well-established link (for a review, see Rudolph & Asher, 2000). These models alternately view peer difficulties as indicators, antecedents, or consequences of maladjustment and psychopathology.

An incidental model (Parker & Asher, 1987) frames peer disturbances as a by-product of underlying pathogenic processes arising from genetic or early environmental factors. According to this model, peer relationships serve as a detection system that indicates the presence or absence of

psychopathology, a type of litmus test for children's general well-being. Disturbances in the peer system are believed to reflect early risk and ensuing emotional and behavioral maladjustment. Within this model, the observed association between early peer difficulties and subsequent psychopathology is considered an epiphenomenon resulting from developmental continuity in adjustment. This model does not discount the importance of peer difficulties—indeed, they are viewed as key markers of risk for mental health problems—but rather assumes that peer disturbances themselves are not making an active contribution to subsequent psychopathology.

Although the peer system likely does serve as an effective detection system for underlying disturbances, contemporary causal models view early peer difficulties as active contributors to subsequent psychopathology (Choukas-Bradley & Prinstein, 2014; Parker et al., 2006). Consistent with a developmental psychopathology perspective, these models emphasize the role of peer relationships in the context of normative and atypical development. Whereas healthy peer relationships serve as positive socialization forces that enhance normative development, unhealthy peer relationships serve as negative socialization forces that foster psychopathology. Considering that youth learn critical age-appropriate competencies in the context of the peer group, those who are marginalized from such relationships or who experience relationship adversity would fail to develop the necessary resources to maintain healthy developmental trajectories and would not benefit from the health-promoting effects of positive relationships (Parker et al., 2006). Moreover, the peer group can act as a direct source of deviant influence that heightens risk for psychopathology (Prinstein & Dodge, 2008). Causal models therefore view peer group experiences as direct or indirect contributors to mental health.

Over the past two decades, theories of peer-psychopathology linkages have become increasingly sophisticated. Recent models consider how youth and their peer environments jointly contribute to psychopathology by incorporating ideas about interactive processes (e.g., peer disturbances predict the most severe psychopathology in youth with preexisting vulnerabilities; Rudolph, 2009) as well as transactional processes (e.g., early behavioral disturbances set in motion adverse peer processes, which then perpetuate and exacerbate risk; Dishion, 2014). According to these models, disruption within each risk domain (interpersonal and intrapersonal) and interactions among domains gain momentum over time, setting youth upon a developmental trajectory to disorder. Causal models, in sum, approach peer group experiences as making direct or indirect contributions to mental health. In the ensuing discussion of peer-oriented theories, we first consider the interpersonal nature of peer social ecologies (close bonds, broader social networks, and status in the peer group) and then move on to the intrapersonal motivations that drive these social relationships.

Theories of the Peer Ecology

Theoretical Underpinnings. As within families, peer ecologies operate at multiple levels and exert both direct and indirect socialization influences on the development of psychopathology. Without a natural attachment figure, peer social ecologies do not come pre-established with a secure base. Nonetheless, such bases for safety and support can be found among peers in the form of friendships. Friendship is the foundational interpersonal tie within the peer group. High quality dyadic friendships are of great comfort and significance (Bukowski, Motzoi, & Meyer, 2009; Hartup & Stevens, 1997; Ladd, 2005). However, peer relations can vary in the type of interpersonal tie they concern—friendships, affiliations, liking, even antipathy—and in the number of individuals involved. Influence flows through these multidimensional social networks of interpersonal affiliations.

A defining characteristic of peer relations is that of equality (Bukowski, 2011; Hartup, 1983; Sullivan, 1948/1953), but such is the nature of society that status is rarely equally distributed among all (Moreno, 1932). Children come to recognize the importance of social status, to more or less prioritize its attainment in their lives (LaFontana & Cillessen, 2011; Rodkin, Ryan, Jamison, & Wilson, 2012), and to both adapt and attempt to increase their place in the social order. Status differentials are another basic channel through which influence flows (Brechwald & Prinstein, 2011).

We elaborate on these two interrelated axes of peer social ecologies (Rodkin, 2004; Rodkin & Gest, 2011)—*social networks* and *social status*—with an eye toward understanding their contribution to the development of psychopathology. Exploration of these ideas reveals the multifaceted and often paradoxical effects of peer relationships on mental health. Phenomena of social networks and social status surround children whether they move toward, against, or away from the world (Caspi, Elder, & Bem, 1987). Even children who feel negatively toward society or toward their peer cohort can find and construct niches of interpersonal support. From the standpoint of the child coping with the stressors of living, a welcoming social network may be an unmitigated resource. From

the standpoint of the developmental psychopathologist, concerned with long-term trajectories of youth, network influences can vary dramatically, attenuating or exacerbating adjustment problems. The type of friendships and networks in which youth participate can determine their salutory versus toxic effects; youths' position within their peer groups can determine their access to resources, which can serve as either risk or protective factors. Even youth with high social status may be susceptible to adverse influence, engaging in risky activities, and the temptation to abuse their status by harassing others.

Social Networks The dyadic friendship is the starting point of any discussion of peer social networks. Many have written on the features of friendships (Bukowski et al., 2009; Hartup & Stevens, 1997; Ladd, 2005; Parker et al., 2006; Rubin et al., 2006), which include reciprocated liking, an egalitarian relationship characterized by cooperation, and similarity in at least some aspects of affect and behavior. Friends provide each other with emotional support, validation, tangible assistance, and enjoyment. Within-species friendships may have an evolutionary function and significance just as has been posited in classical attachment theory (Seyfarth & Cheney, 2011).

Many have theorized that simply having a reciprocal or close friend can protect against the hazards of everyday life, thereby reducing risk for psychopathology (Ladd, 2005). Indeed, having a best friend present during a negative experience can dampen the deleterious effects of that experience on self-worth and HPA activity (Adams, Santo, & Bukowski, 2011) and protect against dysregulated cortisol patterns in youth who face exclusion by peers (Peters, Riksen-Walraven, Cillessen, & de Weerth, 2011). Yet Hartup and Stephens (1997) noted that it is informative to know not simply whether a child has a friend but also the identity and behavioral characteristics of these friends and the quality of the friendship. We return to these topics when considering the role of social networks in specific forms of psychopathology.

Antipathy, or relationships of mutual dislike, can be seen as akin to the opposite of friendship. Antipathy is a natural human feeling, surely not to be celebrated, but not to be pathologized either. At the same time, it is obvious that strong currents of dislike running through peer social networks is trouble waiting to happen. Although controversial, asking children whom they like least reveals information that the absence of liked most nominations simply cannot. The liked least question was critical to the sociometric status categories of Coie, Dodge, and Coppotelli (1982) and is central to a literature on children's antipathies, or mutual nominations of dislike (Hodges & Card, 2003). Card's (2010) meta-analysis of studies of children's antipathies revealed three findings: (1) approximately 35% of children and adolescents have an antipathetic relationship; (2) antipathies are associated with externalizing and internalizing problems; and (3) almost half of children's mutual antipathies are mixed-gender, between a boy and a girl (see also Rodkin, Pearl, Farmer, & Van Acker, 2003). An antipathetic relationship between two children can lead to negative thoughts about the other, such as hostile attributional biases, as well as to negative behaviors, such as aggression (Peets, Hodges, & Salmivalli, 2008), possibly laying the groundwork for emerging psychopathology in both members of an antipathetic dyad.

Social ties involving more than two individuals can be conceptualized as a more complex social network. The most common type of network studied involves friendships, but networks can be organized around a variety of social ties beyond friendships, such as whom children hang around (Rodkin & Ahn, 2009), want to be like, or even do not like (Berger & Dijkstra, 2013). In a broad review of social dynamics within networks, Rivera, Soderstrom, and Uzzi (2010) make a distinction between three types of mechanisms that unite individuals into groups: (1) assortative, centered on the importance of individuals' attributes (e.g., social behavior, personality, ethnicity, gender); (2) relational, emphasizing the importance of existing relationships in the network—some ties in a social network come to exist because of social ties that already exist; and (3) proximity, focused on aspects of physical organization, such as propinquity (e.g., being neighbors).

Theories concerning youth social networks can be considered analogous to a quantitative mapping of microsystemic processes. Building on early studies of sociometry, which quantified properties of peer social ecologies in relation to success and failure, developmental scientists have long been interested in understanding how youth sort into social networks as well as how these networks influence development, including risk for psychopathology (for reviews, see Prinstein & Dodge, 2008; Veenstra & Steglich, 2013). A well-documented phenomenon in social networks is *homophily*, or the tendency for youth to affiliate with similar peers (McPherson, Smith-Lovin, & Cook, 2001).

Theorists also emphasize the concept of complementarity or an opposing tendency to have differentiation in group skills or roles (Farmer et al., 2002). It makes sense that in well-functioning groups individuals will share some characteristics and attitudes while having unique skills. Homophilic processes may differ for particular types of ties (e.g., friendships, affiliations) and behavioral types

(e.g., aggression, substance use, depression; Brechwald & Prinstein, 2011). Social network theory proposes several processes through which similarity might emerge: (1) active selection processes (e.g., an active or affirmative preference or birds of a feather flock together effect—the tendency for individuals to select like-minded friends); (2) passive or default selection processes (e.g., a marginalization effect—marginalization from a mainstream network and losing positive ties with normative others leaves only social isolation or affiliation with other marginalized peers; Choukas-Bradley & Prinstein, 2014; Van Zalk, Kerr, Branje, Stattin, & Meeus, 2010a); and (3) peer influence processes—peers socialize network members to adopt similar beliefs and behaviors through reinforcement, modeling, internalization, and group identification, such that network members become more similar over time (Prinstein & Dodge, 2008). Socialization mechanisms could vary according to the extent of group identification, which promotes internalization of, and not just compliance with, group norms.

The selection vs. socialization antithesis resembles the incidental vs. causal models of peer influence outlined at the opening of this section: Is homophily due to interpersonal influence, or were youth already similar before they started getting to know one another? Disentangling selection from socialization is a longstanding pursuit with respect to peer influences on risk-related behavior and is filled with methodological complications. Moreover, when friendship ties are embedded, as they most often are, in a larger social network, then endogenous network processes are potential confounds. That is, social networks entail structural characteristics and mechanisms that are inherent to any social system, including network closure, the well-known phenomenon that friends of friends are likely to become friends in the future; reciprocity, the tendency for unilateral perceptions, such as of friendship, affiliation, or enmity, to eventually be returned; density, the proportion of interconnected ties within a social network; and hierarchy or centralization, the degree to which social capital (e.g., friendship nominations) is centered upon a small, favored few or distributed in a more broad and egalitarian manner throughout the network. Contemporary longitudinal social network modeling techniques allow selection and socialization processes to be assessed net of these endogenous phenomena (Veenstra & Steglich, 2013).

Social Status Despite the egalitarian connotations of the word *peer*, not all social niches are created equal. Just as there can be a large variety of ties that connect youth into social networks, status can be considered along a number of dimensions. Children and youth differ in their material resources, physical attractiveness, physical size and strength, athleticism, and other peer-valued characteristics that may have different levels of importance in male and female peer cultures (Adler & Adler, 1998; Maccoby, 1998). The classic measures of social status have been the number of children's friendships (e.g., Sherif, 1956) or the number (or proportion) of peers nominating or rating a child as someone whom they like the most (Moreno, 1934).

Coie et al. (1982) proposed an influential framework where the difference between acceptance and rejection (i.e., liked least nominations) formed a measure of social preference, which in turn was considered with the sum of acceptance and rejection (termed *social impact*) to yield various sociometric categories: popular, controversial, rejected, neglected, average (and unclassifiable). This taxonomic system focused only on positive and negative nominations, disregarding social network ties between peers (Cairns, Leung, & Xie, 1998). Of the five sociometric categories, the rejected grouping received by far the most attention from a developmental psychopathology perspective. Indeed it is safe to say that the research attention focused on the peer-rejected child represented the effective entrée of peer relations research to the modern discipline of developmental psychopathology (e.g., Coie et al., 1992). Who are peer-rejected children? Rejected children, those who are widely disliked and hardly liked, have varied behavioral profiles—many are aggressive, more still are anxious and withdrawn (French, 1988, 1990)—but they clearly are at risk for concurrent and future adjustment problems. Sometimes, though not a traditional concern of developmental psychopathology, children are excluded because of the group to which they belong, be it a gender or racial group (Killen, Mulvey, & Hitto, 2012). Peer rejection is the construct around which incidental versus causal models of peer relations for later maladjustment were constructed by Parker and Asher (1987). The 1990 edited volume, *Peer Rejection in Childhood* (Asher & Coie, 1990), delineated many of the challenges that rejected children face, and set in motion a focus on prevention that continues to form a critical corpus in peer relations research (Bierman, 2005; Prinstein & Dodge, 2008).

It seems sensible enough to equate dislike with peer rejection, but problems become evident when popular children are defined as the most liked and least disliked, as they were in the Coie et al. (1982) system. As described in our developmental significance section, at some point, be it middle childhood or early adolescence (Rodkin et al., 2012), children come to differentiate being likeable (or preferred) from being popular. Preference expresses a personal sentiment (i.e., who do *you* like?),

but popularity represents a judgment about what others value and the consensual norms of the peer ecology. Children high in preference have an untroubled set of behavioral characteristics—cooperative, friendly, prosocial, nonaggressive, and sociable (Rubin et al., 2006)—and so they were never much focused on in developmental psychopathology research of the 1980s and 90s. In contrast, popularity has only modest (in some cases positive, in other cases negative) correlations with aggression (Rodkin & Wilson, 2007; Rodkin et al., 2000). Neal (2010) suggested that distinctions between preference and popularity are especially important for socially aggressive behaviors such as relational aggression (Crick et al., 1999).

Some popular youth, or youth hoping to be popular, want to publically demonstrate their social prowess and avoid the pitfalls of social vulnerability, even if this means resorting to aggressive and antisocial behavior. Popular children, because of their heavy engagement in social networks, might be highly susceptible to social influence from peers (Haynie, 2001). They may be tempted to abuse their high social position by bullying peers, demonstrating their dominance through harassment and humiliation. They may devalue academic efforts, as budding scholars, nerds, and straight A students rarely have high social status unless they are also attractive and athletic (Coleman, 1961). In sum, although low social status is well-known as a potential marker of poor adjustment, youth with high social status are not invariably well adjusted.

Developmental Significance and Change. Peer social ecologies begin small but get larger and more differentiated with time, and are shaped by institutional structures, such as daycares and schools. The importance of social networks can be seen even at the earliest ages of nursery school (e.g., Merei, 1949). Schaefer et al. (2010) considered fundamental properties of social network formation over a school year and found evidence for a cascading mechanism in which a simpler network process, such as reciprocity, emerged before the establishment of a more complex network process, namely status hierarchies, which in turn emerged before still more complicated network processes such as triadic closure. Thus, Schaefer et al. (2010) provide support for the proposition that popularity becomes increasingly important for the structure of preschoolers' interactions throughout the school year. By the ages of four and five, children are highly susceptible to peer influence (Haun & Tomasello, 2011).

Some of the most innovative work on social status and its behavioral correlates has occurred with preschool children. Roseth, Pellegrini, Bohn, Van Ryzin, and Vance (2007) reported that some preschool children use aggression effectively to establish social dominance, and that once a social order is established, overt aggression tends to decrease. Some high status preschoolers and adolescents, termed *bistrategic controllers*, can flexibly employ aggressive and prosocial strategies to achieve instrumental aims (Hawley, Little, & Card, 2007).

White (1996) called the biological, psychological, and social transition between the ages of 5 and 7 an entry into an age of reason, when children become especially open to assimilating the traditions and demands of society. It is during this age when formal schooling begins and theory of mind comes into play. White (1996) saw the 5-to-7 shift as intrinsically neurobiological, including the completion of myelinization across major circuits in the body, cortical energy consumption peaks, stabilization of electroencephalographic rhythms into an adult pattern, and more. Konner (2010) notes the evolutionary relevance of middle childhood, a period of life unique to our species, to the development of the human capacity for social relations and cognitive growth. Indeed, Piaget (1932) saw this time as the beginning of heteronomous morality (i.e., moral judgments based more on inferences of intent than the severity of outcomes) and the beginning of cooperative, collaborative social relations. Maccoby (1998) noted that by 7 years of age the two cultures of male and female peer groups are firmly in place, when children are ready to learn society's rules about gender roles and social status more broadly.

Middle childhood peer social ecologies are highly developed, and preadolescents engage in a gamut of relational ties. It is during middle childhood that Sullivan (1948/1953) wrote of the great, protective powers of a chum. Children form antipathies (Card, 2010), affiliative social networks (Cairns & Cairns, 1994), and groups with a strong sense of identity that can influence behavior and moral judgment (Killen & Rutland, 2011). Social status continues to be an axis of the peer social ecology during middle childhood. By fifth grade, popularity is a prime organizing force of children's social networks, perhaps more influential in determining affiliative homophily than aggressive or prosocial behavior (Dijkstra, Berger, & Lindenberg, 2011; Logis, Rodkin, Gest, & Ahn, 2013). Pre- and early adolescent children describe popular boys as cool, athletic, funny, and defiant, and popular girls as attractive, sociable, snobby, mean, and rude. Not surprisingly, unpopular children have particularly negative attitudes toward their popular peers (Adler & Adler, 1998). Although boys and girls may express negativity in different ways, dominance-related beliefs and behaviors are related to positive peer regard for both girls and boys (Hawley, Little, & Card, 2008).

Hawley et al.'s (2008) myth of the alpha male is that girls too can strive for a balance between prosocial and coercive interpersonal strategies in search of a dominant position in the peer group (see also Crick et al., 1999). By the late elementary school years, the differences described earlier between preference and popularity become more easily distinguishable (Rodkin et al., 2012). The behavioral correlates of popularity change from being relatively more prosocial early in development to relatively more aggressive as youth reach adolescence (Cillessen & Mayeux, 2004).

Peer social influence is often thought to be at its apex during adolescence, when youth crave attention and status (LaFontana & Cillessen, 2010), are easily swayed into deviant peer groups, and form an adolescent culture (Mintz, 2004). Indeed, during adolescence, peer relationships become a highly salient source of socialization and self-evaluation (Choukas-Bradley & Prinstein, 2014). By adolescence, status differences appear to be quite consequential. *Crowds*, which may be a type of social relationship particular to adolescence in the modern high school, are groups that are based on reputation, not necessarily affiliation or friendship (Brown & Dietz, 2009). Youth who are identified by their peers or themselves as belonging to a particular crowd appear to be of the same type. Placement in a crowd identifies youth as engaging in certain behaviors but also can denote ethnicity, class, and social status. As with peer groups and friendships, however, effects of crowd membership on adjustment will vary depending on the kind of crowd it is, and possibly how crowd membership overlaps with friendship and other social networks.

In recent years, developmental scientists have increasingly considered how brain reorganization during adolescence may guide further changes in peer relationships (Murray-Close, 2012). Puberty is marked by alterations in physiological systems guiding self-regulation, motivation, and emotion, with accompanying implications for youths' social orientation. For example, Steinberg (2008) proposed that puberty-related changes in the brain's incentive-processing system, driven by alterations in the dopaminergic system, trigger more reward-seeking in the presence of peers and consequent increases in risky behavior. Susceptibility to peer influence and ensuing risky behavior declines between adolescence and adulthood because of maturation in the brain's cognitive control system, which results from structural changes in the prefrontal cortex and its connectivity to other brain regions, along with a decline in reward seeking. Increases in testosterone during puberty also may heighten dominance-related behaviors linked to peer aggression. Furthermore, linkages between sex-linked hormone systems that develop across puberty (e.g., estrogen, androgens) and the HPA axis may trigger developmental changes in peer relations, such as heightened reactivity to peer stressors.

Biologically driven changes may intersect with psychosocial influences across puberty to alter the peer system in ways that influence risk for psychopathology (for a review, see Rudolph, 2014). Somatic changes signal approaching maturity with implications for peer status and selection into particular social networks and crowds. According to the peer socialization hypothesis (Stattin, Kerr, & Skoog, 2011), these effects may be especially salient for youth who mature off-time, particularly early, relative to their peers. Reflecting selection effects, early-maturing youth may seek out friendships and romantic relationships with similarly mature peers, who will be other early-maturing and older youth. Because these youth on average engage in more norm-breaking behavior, early-maturing youth are more susceptible to early risk for antisocial behavior. Thus, biological, psychological, and social aspects of puberty influence and interact with peer selection and socialization processes in ways that can shape trajectories of psychopathology.

During the pubertal transition, sex-typed peer relationship processes also may intensify as a result of differential socialization elicited by signs of physical maturation. For example, Rose and Rudolph (2006) proposed a model wherein immersion in same-sex peer groups early in development contributes to sex-linked behavioral and social-cognitive styles, which interact and transact with sex-linked stress and coping processes within peer relationships to contribute to heightened risk for internalizing psychopathology in girls and externalizing psychopathology in boys. The adolescent transition is presumed to amplify these sex-linked processes, leading to increasing divergence between female and male peer groups. Developmental changes in relationships may be a particular burden for adolescent girls. Although distinctive attributes of adolescent female relationships (e.g., heightened intimacy and disclosure) provide a strong sense of social connectedness and belonging, they also come with some costs. Specifically, girls' focus on connection-oriented goals (e.g., intimacy, nurturance) may be accompanied by heightened vulnerability and strife, especially during adolescence when interpersonal roles and expectations undergo significant redefinition and disruption. Adolescent girls also report higher levels of interpersonal sensitivity, reflected in both concerns about approval, evaluation, and abandonment as well as empathy for others. This stronger interpersonal engagement may heighten the salience and adverse impact of disruption in the peer groups of adolescent girls

compared to boys (Crick & Zahn-Waxler, 2003; Rose & Rudolph, 2006).

Application to Psychopathology. In classical ecological theory, there can be a dystopia and social chaos around the idea of youth forming their own peer social ecologies that are poorly regulated or not regulated by adults. Bronfenbrenner (1979) was clear that peer microsystems were prone to problem behavior, and suggested that the developmental sequelae of accumulated peer group processes, particularly within educational settings, can narrow future life opportunities. It is the recognition that peer ecologies can have a negative influence on children that promotes prevention-oriented research on how to consider ecologies as a malleable factor, and interpersonal relationships such as friendship as a protective factor and source of social capital. Building on this historical perspective concerning the potential adverse influence of the peer group, well-articulated theories have emerged concerning the contribution of peer relations to multiple forms of psychopathology.

Externalizing Psychopathology As Cairns and Cairns (2001, p. 32) stated: "The development of aggressive strategies grows out of close affiliations and relationships, not because of their absence." The risky nature of interpersonal influence among aggressive and antisocial peers is captured in the theory of deviancy training (Dishion, Spracklen, & Patterson, 1996), which explicates the coercive processes that emerge when aggressive children congregate together, contributing to the development of antisocial behavior. Deviancy training occurs when a youth engages in or discusses antisocial behavior and peers reinforce that behavior by granting approval or high status. Other peers are then likely to reciprocate by engaging in antisocial behavior as well. In addition to verbal and nonverbal reinforcement through deviancy training, associating with deviant peers can increase adolescents' own antisocial behavior in very tangible ways by providing opportunities for antisocial behavior. Affiliating with deviant peers also may foster the perception that antisocial behavior is the norm, thereby reinforcing such behavior. Adolescents who associate with deviant peers by the age of 13 are more likely to behave in antisocial ways and use drugs during young adulthood (Dishion & Tipsord, 2011).

Deviancy training may play a particularly important role in the development of antisocial behavior because a group of peers acting jointly is much more likely to engage in antisocial behavior than is a single individual acting alone. The strongest correlate of adolescents' delinquency is the delinquency of their peers (Warr, 1993). Consistent with active selection processes, adolescents who engage in antisocial behaviors select friends who engage in similar behaviors (e.g., McPherson et al., 2001). However, studies that statistically control for the effects of peer selection demonstrate that once antisocial peers are in a group together, they incrementally increase one another's engagement in a wide range of antisocial behaviors including early and high-risk sexual behavior, violent offenses, and substance use (Dishion, 2000). Along these lines, Schulenberg, Patrick, Maslowsky, and Maggs (2014) describe a process of progressive accommodation, wherein adolescents select like-minded friends who engage in alcohol use, who in turn provide strong socialization influences. These negative outcomes even extend to potentially adverse effects of intervention programs that group together antisocial youth (Dishion et al., 1999). Peer network effects can vary by the type of interpersonal tie studied (e.g., peer groups vs. best friendships; Cruz, Emery, & Turkheimer, 2012), gender (Fujimoto, Unger, & Valente, 2012), and the phenomenon under investigation (Brechwald & Prinstein, 2011).

Theories of the deviant peer group were originally quite constrained to deal with adolescents. In early classic conceptualizations, children who engage in coercive cycles of violence with their caregivers during early childhood and who then generalize these dysfunctional interactional patterns upon entering school become rejected and set up for academic failure, falling through the cracks until forming groups, presumably through passive selection or deselection processes, with similarly marginalized (or deviant) youth in adolescence. However, peer deviancy processes have been shown in children as young as first grade, with unique relations to aggressive behavior patterns in fourth grade (Snyder, Schrepferman, Bullard, McEachern, & Patterson, 2012). Even in early childhood, social networks are multidimensional, and so it is possible for children to be widely rejected but to have a friend, or to lack a reciprocated friend but be part of an affiliative peer group (e.g., Kinderman, 2007). Social network effects stemming from the absence of peer support (i.e., peer rejection) and the presence of peer support (i.e., affiliative peer groups) can operate concurrently and have cascading effects over time.

There also is some question as to whether the kinds of processes specified to operate among deviant peers are limited to cases of deviance. Dysfunctional deviant peer group processes have in fact some functionality. Dishion (2014, p. 458) argued that deviant peer clustering can be viewed as "an evolutionary-based adaptation to marginalization and stress in families and the school environment" that emerges in part from "the biologically driven survival

function of procreation and group affiliation." The mechanisms involved in deviancy training—laughing, smiling, reinforcing, or granting high status to the peer who engages in antisocial behavior—are by no means restricted to a small subgroup of already at-risk children. These same processes are implicated in discussions of why youth bully. As Olweus (1979) noted, some bullies are socially integrated and networked (see also Rodkin, 2011). These youth affiliate with a wide variety of peers, in which case there is an unhealthy potential for widespread acceptance of bullying in some classrooms and schools. This is what Pepler and colleagues call the theater of bullying (Pepler, Craig, & O'Connell, 2010), encompassing not only the bully–victim dyad but also children who encourage and reinforce bullies (or become bullies themselves), others who silently witness harassment and abuse, and hopefully still others who intervene to support children being harassed (see also Salmivalli et al., 2010). As Pepler and colleagues (2010, p. 470) wrote, "Bullying is a social event" with an audience of peers in almost 90% of observed cases. This silent, mocking audience grows exponentially, in frightening anonymity, with cyberbullying (Rodkin & Fischer, 2013). Epitomizing the developmental psychopathology principle of intersections between normal and atypical development, therefore, the mechanisms driving the acceptance of aggression in deviant peer groups may in fact be deeply rooted and broadly based.

Indeed, there is still some question as to whether bullying is a form of psychopathology rather than an instance of normative development (Dodge & Albert, 2012), but there is a more widespread consensus that high social status, and not just low social status, is a relevant construct to the developmental psychopathologist (Dodge & Albert, 2012; Ellis et al., 2012). It is still relatively new to consider high social status as an attribute that could contribute to any form of psychopathology, including externalizing problems. However, evidence is accumulating that popularity, like unpopularity, can be a risk factor associated with drinking (Crosnoe, 2006), smoking (Mayeux, Sandstrom, & Cillessen, 2008), and disruptive and aggressive behavior (Lansford et al., 2009). Linkages between popular-aggressive youth and Moffit's (1993) adolescence-limited trajectory seem clear, but there has been no formal comparison in the literature and empirical linkages between social status and aggression have often been reported in the pre-adolescent years (Rodkin et al., 2000). Causal linkages between low social status—peer rejection or isolation—and aggressive behavior, one of the most studied topics of peer relations scholarship, play a central role in the most influential frameworks for understanding childhood aggression, such as dynamic cascade models (e.g., Bierman, 2005; Dodge, Greenberg, Malone, & the CPPRG, 2008; Dishion & Tipsord, 2011; Lansford, Malone, Dodge, Pettit, & Bates, 2010).

Depression and Anxiety Developmental scientists are becoming increasingly interested in characterizing the peer worlds of youth with internalizing symptoms in an effort to understand how adverse conditions contribute to risk as well as how symptoms interfere with the maturation of normative peer relationships. Although it has long been argued that healthy peer relationships can serve as protective forces in development—buffering youth with risks due to genetic liability, tumultuous family circumstances, and the like—contemporary theoretical perspectives have turned to mapping out the possible dark side of peer relationships for youths' emotional health (Choukas-Bradley & Prinstein, 2014; Rose & Rudolph, 2006). Later, we describe the adverse effects of specific stressors within peer relationships (rejection, victimization, exclusion). In this section we discuss other aspects of youths' peer ecologies that may contribute to risk for internalizing symptoms.

At a dyadic level, failure to develop intimate friendships can cost youth the rewarding provisions of enjoyment, support, and trust that protect against emotional distress. It is not surprising that anxious and depressed youth have poorer quality friendships and are members of smaller social networks, thereby undermining their access to such resources (for reviews, see Choukas-Bradley & Prinstein, 2014; La Greca, Davila, Landoll, & Siegel, 2011). Exposure to friendship conflict and dissolution or friendlessness can contribute to internalizing symptoms (Davila et al., 2010; La Greca et al., 2011; Rudolph, 2002) and, in turn, symptoms can further interfere with the establishment of close and supportive friendships (Davila et al., 2010; La Greca et al., 2011).

Beyond poor access to resources or the pathogenic effects of conflictual relationships, however, unhealthy processes may emerge even within the context of relatively healthy or close friendships. Rose (2002) proposed that corumination, a process wherein friends frequently and extensively discuss their problems, may heighten closeness but also contribute to anxiety and depression by focusing attention on negative affect and stress. Moreover, corumination occurs more often in adolescent female than male friendships and predicts anxiety and depressive symptoms in girls but not boys, perhaps helping to account for girls' higher levels of internalizing symptoms (Rose, 2002). Giletta and colleagues (2012) distinguished best friendships and friendship networks in a study of peer socialization of alcohol use and depressive behaviors in

ninth through eleventh grades. They found that network effects were stronger for the socialization of alcohol use, but for girls there was additional socialization of depressive behaviors within best friendship dyads.

The growth of sophisticated approaches to social network analysis also has spurred an interest in deconstructing the phenomenon of homophily for social network members sharing similar levels of symptoms (Prinstein, 2007). This work aims to determine whether homophily arises through peer selection or influence as well as to identify underlying processes. Several mechanisms may drive selection effects in the networks of depressed youth (for a review, see Schaefer, Kornienko, & Fox, 2011). Consistent with a misery loves company scenario, homophily may arise through active selection into friendships or peer groups with other depressed youth, perhaps due to preference for similar others or negative feedback seeking. Homophily also may result in dissolution of relationships with dissimilar friends (Kiuru, Burk, Laursen, Nurmi, & Salmela-Aro, 2012). Alternatively, depressed youth may sort into groups through default selection when other friendship options are constrained. Depressed youth show many unappealing characteristics as interaction partners and friends (e.g., excessive reassurance seeking, hostility, poor conflict resolution); being friends with depressed youth may therefore be unpleasant and stigmatized. Indeed, depressed youth elicit negative reactions from peers (for a review, see Rudolph, Flynn, & Abaied, 2008) and are less likely to be selected, and more likely to be deselected, as friends over time (Van Zalk et al., 2010a). Conflict with friends and exclusion by the mainstream peer group may lead them to seek out other depressed youth. Beyond this active peer exclusion, social withdrawal may cause depressed youth to detach from peers, marginalizing themselves in the social system and thereby leaving only an impoverished pool of other depressed youth as viable interactional partners (Schaefer et al., 2011). Consistent with this idea, youth with depressive symptoms are more likely to deselect friends over time (Van Zalk et al., 2010a), thereby leading to social isolation.

Homophily in internalizing symptoms also may stem from peer influence processes, wherein youth become more similar to their network members over time. The dynamics of peer influence may differ depending on the underlying processes. Direct contagion could occur if friends overtly encourage or adopt one another's depressive affect and behavior (Coyne, 1976; Kiuru et al., 2012). One might imagine a similar process occurring in the networks of anxious youth, as heightened worry and arousal spread among friends. Indirect contagion could operate in a more subtle way through adoption of group norms to obtain acceptance or status (Kiuru et al., 2012), negative affect induced by excessive reassurance seeking (Joiner & Timmons, 2009), absence of enjoyable social interactions between friends, or shared exposure to depressed friends' problems. Peer selection and influence processes are embedded within a broader set of dynamics driving the coevolution of social networks and depressive symptoms composed of individual level effects (personal risk factors), depression feedback (the self-perpetuating nature of symptoms), and endogenous network processes (Schaefer et al., 2011).

Research confirms that peer selection, deselection, and influence all contribute to depression homophily within friendship networks (Kiuru et al., 2012; Schaefer et al., 2011; Van Zalk et al., 2010a), with particularly strong effects for girls (Van Zalk, Kerr, Branje, Stattin, & Meeus, 2010b); social network effects also emerge for related internalizing psychopathology such as anxiety (Mercer & DeRosier, 2010) and self-injury (Prinstein et al., 2010). There is some indication that peer selection occurs through a process wherein depressed youth withdraw from peer relationships, resulting in affiliation with other marginalized youth; thus, depression homophily may occur as an endogenous product of other network forces rather than through a preference effect (Schaefer et al., 2011). With regard to peer influence, there is evidence for a convergence effect in which youth develop depressive symptoms at levels comparable to those in their networks (i.e., youth become either more or less depressed over time to resemble the average symptom level of their peers), leading to increasing similarity within networks (Kiuru et al., 2012). Peer influence effects may be due in part to co-rumination (Schwartz-Mette & Rose, 2012) and transmission of negative cognitions (Stevens & Prinstein, 2005; Van Zalk et al., 2010b) among friends. Such findings highlight the importance of distinguishing peer selection and influence mechanisms driving the structure and evolution of social networks. Moreover, youth may be differentially sensitive to depression contagion effects (Prinstein, 2007), suggesting the need to consider individual differences in these processes.

At the level of the broader peer group, it is intuitive that high social status should serve a protective function against internalizing symptoms. However, a more nuanced perspective on risk has emerged as contemporary theories have distinguished likeability or peer preference from popularity (Sandstrom & Cillessen, 2006), as discussed earlier. Low peer preference is associated with more depressive symptoms (Zimmer-Gembeck, Waters, & Kindermann, 2010), especially in girls (Oldehinkel, Rosmalen, Veenstra, Dijkstra, & Ormel, 2007), perhaps because of the psychological implications (e.g., loneliness,

low self-esteem) of being isolated from the social group (Oldehinkel et al., 2007) along with the distinct affiliative needs of girls (Rose & Rudolph, 2006). However, popularity may harbor its own emotional costs, particularly for popular girls who are viewed in more negative ways by peers than popular boys (Rose, Glick, & Smith, 2011).

Eating Pathology Risk-related changes in body image and eating behavior often emerge in the context of the pubertal transition, a stage during which peer influence becomes pronounced as adolescents increasingly rely on the judgments of peers. Puberty brings about physical changes that are open to scrutiny by peers and are often subject to commentary and harassment (Rudolph, 2014). Adolescents who fail to meet the ideal norms for their gender (thinness for females; lean muscularity for males) may be especially sensitive to social conformity pressures, aiming to meet explicit or implicit social norms and to reduce discrepancies between themselves and their peers (Rancourt, Conway, Burk, & Prinstein, 2012). In this way, peers can serve as active agents in the socialization of eating pathology by modeling and reinforcing group-endorsed attitudes (e.g., body image concerns) and behaviors (e.g., dieting, excessive exercise, muscle gaining). Of note, the gender composition of peer groups may moderate these peer influence processes, such that belonging to a same-gender peer group enhances socialization effects (Rancourt et al., 2012). Of course, youth also may show a preference for befriending peers of a similar weight; in particular, overweight youth may be stigmatized and marginalized by peers thereby creating strong selection (or de-selection) effects (de la Haye, Robins, Mohr, & Wilson, 2011).

Socialization also may occur within the context of specific adolescent crowd affiliations. For example, affiliating with Brains is associated with more healthful eating and dieting, whereas affiliating with Popular and Burnout crowds is associated with more unhealthful eating and, for the latter, food preoccupation/bulimic behaviors (Mackey & La Greca, 2007). However, processes of peer selection versus influence within these crowds have not yet been disentangled through longitudinal analysis, making it difficult to determine whether affiliating with certain crowds promotes change in eating attitudes and behaviors or whether youth gravitate toward crowds with similar norms in this domain.

Social Motivation Theories

Theoretical Underpinnings. The human needs of belonging, acceptance, affiliation, and influence are basic motivational strivings (McClelland et al., 1953). All involve interpersonal relationships—we wish to be accepted by others, to affiliate with others, to influence others. To fulfill these needs, children develop specific goals for social interaction (e.g., nurturance, intimacy, companionship, domination; Rodkin & Ryan, 2012), cognitive representations of what they want to accomplish, which provide direction and energy for behavior.

Both classic (McClelland et al., 1953) and contemporary (Dweck & Leggett, 1988; Gray, 1994) theories of motivation suggest that individual differences in behavior are regulated by two systems: an approach (appetitive) system, sensitive to reward or success, and an avoidance (defensive) system, sensitive to punishment or failure. Approach-avoidance dispositions are manifested across many domains, including temperament, personality, affect, and coping (Gable, Reis, & Elliot, 2003). As such, approach and avoidance motivation are embodied in terms of general needs or strivings as well as more specific goal orientations that underlie and shape behavior. Within the interpersonal sphere, social approach motivation involves sensitivity to social rewards (e.g., obtaining social approval, positive judgments, acceptance, status, intimacy) whereas social avoidance motivation involves sensitivity to social punishments (e.g., avoiding social disapproval, negative judgments, rejection, loss of status, alienation) (Rodkin et al., 2012; Rudolph, Abaied, Flynn, Sugimura, & Agoston, 2011; Rudolph & Bohn, 2014; Rudolph et al., 2005; Rudolph, Troop-Gordon, & Llewellyn, 2013; Ryan & Shim, 2008).

At a dispositional level, children may be motivated by general strivings toward achieving social success or avoiding social failure. As one example, need for approval has been conceptualized as a motivational striving through which children are driven by a desire to obtain positive judgments by peers that enhance their self-worth (approach oriented; e.g., feeling proud of oneself in the face of approval) or to avoid negative judgments by peers that deplete their self-worth (avoidance oriented; e.g., feeling ashamed of oneself in the face of disapproval) (Rudolph & Bohn, 2014; Rudolph et al., 2005). Approach-oriented need for approval is viewed as driving an adaptive orientation toward the world that promotes positive engagement (prosocial behavior, peer acceptance) and suppresses conflictual engagement (aggression, victimization) and disengagement (withdrawal, exclusion). Avoidance-oriented need for approval is viewed as driving a maladaptive orientation toward the world that suppresses positive engagement, promotes disengagement, and may

promote some forms of conflictual engagement such as relational aggression (Rudolph & Bohn, 2014).

General social motives or strivings may, in turn, be translated into specific goal orientations. Youth with a strong approach-oriented need for approval may endorse goals that focus on eliciting signs of approval from peers (i.e., approach goals) whereas youth with a strong avoidance-oriented need for approval may endorse goals that focus on avoiding signs of disapproval from peers (i.e., avoidance goals) (Rudolph & Bohn, 2014). Drawing from achievement goal theory (Dweck & Leggett, 1988), researchers (Elliot, Gable, & Mapes, 2006) have conceptualized social goals within a similar framework that distinguishes developing competence (i.e., mastery goals) versus demonstrating competence (i.e. performance goals).

Reflecting one type of approach motivation, *social mastery (development)* goals involve improving relationships and social skills (e.g., gaining insights into friendships or learning how to get along with others). With social mastery goals, intrapersonal standards are used for evaluating one's competence and judging whether involvement in a relationship is valuable. The motivation for building relationships and forging connections with others is distinct from any specific reward such as status. Success is judged by whether one is improving social skills, deepening the quality of one's relationships, or developing one's social life in general (Rodkin et al., 2012; Rudolph, Abaied et al., 2011; Ryan & Shim, 2008). This goal is similar to what Ojanen, Grönroos, and Salmivalli (2005) term a *communal* goal orientation. Social goals that pertain to developing relationships tend to be associated with prosocial behavior (Rodkin et al., 2012; Rudolph, Abaied et al., 2011).

With social performance (demonstration) goals, interpersonal standards are used for evaluating one's competence and judging whether a relationship is valuable. Attention is focused on one's self, and the reason for effort is to demonstrate competence or self-worth (Rodkin et al., 2012; Rudolph et al., 2012; Ryan & Shim, 2008). This goal is similar to what Ojanen and colleagues (2005) term an agentic goal orientation. Performance goals can be further distinguished along the approach-avoidance dimension. Social performance-approach goals involve garnering positive feedback and gaining social status (e.g., being seen as cool or popular); social performance-avoidance goals involve avoiding negative judgments from others and losing social status (e.g., not being seen as a geek or a loser). Success is evaluated in terms of having a good reputation and high social status for a performance-approach goal, and in terms of avoiding a reputation as socially awkward or ineffective for a performance-avoidance goal. Social performance-approach goals tend to be associated with more aggression whereas social performance-avoidance goals tend to be associated with less aggression and more passive behavior (Rodkin et al., 2012; Rudolph, Abaied et al., 2011).

Developmental Significance and Change. Mapping onto social mastery versus social performance goals, adolescents clearly distinguish who is preferred, with its basis in affiliation and intimacy, from who is popular, with its roots in power and influence (Bukowski, 2011). Although distinctions among goals of affiliation versus status or intimacy versus power may be most salient during adolescence, research reveals clear goal structures as young as fifth grade (Ojanen et al., 2005; Rodkin et al., 2012) and even second grade (Rudolph, Abaied, et al., 2011). Moreover, the behavioral correlates and consequences of social goals appear similar across different ages (Rodkin et al., 2012; Rudolph, Abaied et al., 2011; Ryan & Shim, 2008), suggesting developmental uniformity in the meaning and implications of these goals. Overall, relatively little research has directly investigated developmental continuity and change in social motivation, an area much in need of attention. In this context, it is important to consider the possibility that puberty-driven changes in the neural substrates underlying reward systems (Forbes & Dahl, 2005) result in increasing shifts toward approach motivation during adolescence—whether those shifts are toward a focus on mastery and intimacy or toward a focus on dominance and status may be determined by characteristics of youth and the contexts in which their goals develop (peer groups, classrooms) prior to or during the pubertal transition, suggesting a potential window of opportunity for intervention.

Application to Psychopathology. Motivation has emerged as a key component of many interpersonal theories of psychopathology. In some theories, motivation is viewed from a social-information processing perspective, with a focus on identifiable goals and attributional biases presumed to drive behavior. In other theories, motivation is instantiated in neurocognitive and neural biases presumed to reflect dimensions of temperament or personality. Common across these perspectives runs the idea that motivation may guide individuals' movement toward, against, or away from the world (Caspi et al., 1987).

Externalizing Psychopathology Aggressive children, particularly those who are also rejected, have a unique motivational stance to many interpersonal relationships,

characterized by hostile attributional biases in the face of ambiguity (Crick & Dodge, 1994), retaliation goals in the face of social obstacles (Troop-Gordon & Asher, 2005), and a high value placed on demonstrating competence and status (Rodkin et al., 2012). Regardless of the precise focus, the motivation of youth with externalizing psychopathology epitomizes an emphasis on approach—moving *against* the world in ways that exert influence, garner power, and optimize one's position in the peer group.

Evolutionary and ethological theories form one conceptual backdrop for understanding how social motivation relates to aggression. Aggression, like its close cousin attachment, has deep phylogenetic roots (Cairns & Cairns, 2001; Ellis et al., 2012). Individuals aggress to get what they want and to change the behavior of others. Peer social structures exist within the boundaries of dominance hierarchies, in which some members are more central, popular, powerful, and likely to control resources than are others. Individuals may gain and maintain status, power, and prestige by using aggression, alone or in combination with more prosocial means of control, to dominate their peers. This may be done, for example, by selectively targeting lower status peers or by bullying in the presence of others who support bullying behavior (Kärna et al., 2011; Veenstra et al., 2010).

Socially integrated aggressors may be motivated by goals that orient them to demonstrate social status (Rodkin et al., 2012). Children who aggress might encourage group members to rally around them, to define themselves by excluding deviants, and to maintain cohesion and identity for their clique (Faris & Felmlee, 2011). Dominance hierarchies are neither static nor stable—there can be, and often is, flux in the hierarchy. This flux can occur as a result of changes in behaviors, interactions, and relationships as members try out new roles, as developmentally normative transitions happen (e.g., movement from elementary to middle school), or as idiosyncratic changes emerge in the group structure (e.g., some children move in or out of the peer group). Thus, children who have moderate levels of social status and children who are attempting to increase their status may be motivated to proactively aggress against others to demonstrate their power, establish their social position, and push others downward.

Socially marginalized aggressors may be motivated by a desire to achieve a status that they lack, or in classic frustration-aggression parlance, to displace the aggression that they receive onto targets whom they perceive as weak. Aggressive and coercive behaviors may be viewed by peers as attempts to establish dominance, thereby triggering peers to respond with aggression of their own (Hanish, Sallquist, DiDonato, Fabes, & Martin, 2012). Those who are most effective in using aggression to gain and maintain power tend to rise in the social hierarchy whereas those who are the least effective fall. In these cases, the psychological processes involved in aggression entail the recognition, though not necessarily an accurate understanding, of who is the target of harassment and of the networks in which aggressors and victims are embedded.

Contrasting with these motivations for proactive forms of aggression, in the form of bullying, Carver, Johnson, and Joormann (2008) provide a theory of risk for impulsive (i.e., reactive) aggression and conduct problems. In particular, they suggest these behaviors stem from an imbalance between the behavioral activation (approach) and behavioral inhibition (avoidance) motivational systems—that is, youth with an overactive approach orientation and an underactive avoidance orientation would disregard social norms or potential consequences of their actions to pursue their own self-interest, increasing the likelihood of impulsivity, aggression, and antisocial behavior. These adverse effects are presumed to be potentiated in the presence of poor self-regulation, as reflected in an inefficient top-down effortful control system. Recent work extends these ideas into a social context, such that aggression is prompted by high levels of sensitivity to social reward (social approach) and low levels of sensitivity to social punishment (social avoidance) in the face of poor self-regulation (Rudolph et al., 2013).

Depression In many ways depression is a disorder of motivation, reflecting an inability to upregulate approach-oriented emotions (positive affect or enjoyment) and behavior (effortful engagement with the environment) and an exaggeration of avoidance-oriented emotions (negative affect) and behavior (withdrawal). Many theories of depression therefore consider the contribution of motivational factors at a behavioral level, such as compromised reward-seeking behaviors (Forbes & Dahl, 2005); a social-cognitive level, such as diminished approach strivings/goals and heightened avoidance strivings/goals (Rudolph et al., 2013); and a physiological level, such as underactivation of brain regions involved in approach and overactivation of brain regions involved in inhibition/avoidance (Davidson, Pizzagalli, & Nitschke, 2009).

Contrasting their theory of risk for externalizing psychopathology, Carver et al. (2008) suggested that depression stems from an overactive avoidance orientation and an underactive approach orientation. According to the theory, poor self-regulation combined with a sensitive reactive avoidance or an insensitive reactive approach system is reflected in cognitive perseveration (e.g., rumination),

absorption in emotions, and consequent depression. A significant amount of research from multiple levels of analysis (behavioral, social-cognitive, physiological) has been devoted to understanding the role of the behavioral activation (approach) and behavioral inhibition (avoidance) systems in depression (for a review, see Carver et al., 2008), with some application of these ideas specifically to approach and avoidance motivation within a social context (Rudolph et al., 2013). Overall, this research supports theoretical frameworks linking low approach motivation and heightened avoidance motivation with depression.

Depression also may emerge from more basic social motivational strivings in youth. For example, a heightened avoidance-oriented need for approval may serve as a risk for depression. Youth whose self-worth is threatened by disapproval may experience more frequent fluctuations in their self-views; moreover, when faced with perceived or actual negative feedback from peers, heightened avoidance-oriented need for approval may foster self-disappointment, shame, and sadness, leading to depression (Rudolph et al., 2005). In contrast, youth who use positive feedback as a source of self-enhancement may be protected from depression. Such youth may focus on rewarding social encounters, discount adverse encounters, and feel less self-doubt and hopelessness; those with a diminished approach-oriented need for approval may fail to receive such benefits and be more prone to depression (Rudolph et al., 2005).

Anxiety Applying Gray's (1994) reinforcement sensitivity theory to the peer context, anxiety (particularly social anxiety) also has been conceptualized with regard to its social motivational underpinnings. This line of thinking has distinguished, in particular, the types of motivation that discriminate different forms of withdrawn behavior in youth (Rubin, Coplan, & Bowker, 2009). Shy, inhibited, or reticent children are believed to suffer from an approach-avoidance conflict in that they are high in both types of motivation (they wish to interact with peers but are inhibited by fear and anxiety). This group is believed to experience heightened internalized feelings of social anxiety and to be at risk for social phobia. Avoidant children are characterized by a combination of low social approach and high social avoidance motivation. Unsociable or socially disinterested children, in contrast to both groups, are low in both types of motivation and, therefore, likely do not experience high levels of anxiety. These groups of socially withdrawn children differ in terms of their short- and long-term risks (for a review, see Rubin et al., 2009), suggesting the importance of integrating social motivation into interpersonal theories of anxiety.

Directions for Future Research on Peer Theories

One potentially fruitful direction for research is to take a more ecological approach to understanding individual-level psychopathology by measuring the mental health of peer settings, quantifying measurement along both social network and social status dimensions. This is both an age-old mission of sociometric research (e.g., Bronfenbrenner, 1944) and an exciting new goal given advances in theories and measures of youth settings (Gest, Osgood, Feinberg, Bierman, & Moody, 2011; Seidman, 2011) together with analytic advances in the estimation of selection and socialization processes (Veenstra et al., 2013). Interestingly, this research goal based in community and social psychology has joined with evolutionarily oriented work on the functionality of behavior patterns, including aggressive and antisocial behavior (Cairns & Cairns, 2001). For example, from their life history approach, Ellis et al. (2012, pp. 605–606) suggested setting-level interventions that consider "proactively how to 'engineer' social networks in early adolescence . . . promoting group structures and behavioral strategies that enable adolescents to earn status for prosocial behaviors . . . and avoiding dynamics that confer social status and peer reward for antisocial behavior." Similarly, Dodge and Albert (2012, p. 627) noted that we should "use our evolved capacity to engineer environments in ways to enhance individual development."

An issue, then, is to encourage adults (e.g., clinicians, educators) to attend productively to issues of status and to promote inclusion and integration into social networks. Mikami, Lerner, and Lun (2010) point out that there also exists a social context of rejection: Children can be rejected for not fitting into peer group norms, due to the reputational biases and stereotypes of the majority, or when classroom social networks are marked by hierarchy and stratification (Ahn, Garandeau, & Rodkin, 2010; Garandeau, Ahn, & Rodkin, 2011). In schools and other settings where youth congregate, social network data could be used to design classroom assignments that mix high-risk and low-risk youth (Ellis et al., 2012), identify incipient peer leaders (Gest et al., 2011), correct unhealthy settings where antipathies outweigh friendships (Gest & Rodkin, 2011), identify when the social norms of a peer ecology support unhealthy behavior, and track along social network lines patterns of diffusion across which spread attitudes, values, and behaviors (Dishion, 2014).

Considering motivations that drive children's social interactions and relationships also may be essential for fully understanding the peer context of psychopathology. How can youth be motivated to behave less aggressively when aggression brings social rewards (Hawley, Little, &

Rodkin, 2007)? How can youth suffering from anxiety and depression be motivated to approach a world in which they perceive few social rewards and are exquisitely sensitive to anticipated, perceived, or actual social punishments? One answer may be to focus more specifically on children's motivations regarding social interaction rather than their observable behaviors.

Integrating ecological and motivational theories, what is needed are syntheses that consider the motivations of youth in tandem with measures of their social status and social network position within their actual peer ecologies. This will help foster theories of the peer context that feature, like in the lifespaces of Lewin and sociograms of Bronfenbrenner, a motivated, goal-directed child with beliefs about peers and the social world interacting with a complex social system of friends, acquaintances, enemies, and others. Psychopathology can enter this system via the child's developing beliefs, stance toward the developing society, whether or not a niche is found, and whether the peers that provide proximal support also promote positive adjustment in the long term.

Stress-Based Interpersonal Theories

Multiple theoretical perspectives emphasize the potent contribution of life stress exposure to the development of psychopathology. These perspectives variously focus on the role of early adversity, recent stress, or a combination of the two. Although life stress theories encompass a wide range of acute and chronic stressors, many either emphasize the impact of interpersonal stressors or involve interpersonal mechanisms through which stress undermines development and heightens risk for psychopathology. As such, many of these theories interface with family- and peer-based theories of psychopathology. We will first describe general conceptualizations of life stress and its role in psychopathology and then turn to disorder-specific and stressor-specific models of risk.

General Stress-Based Theories

Theoretical Underpinnings. The study of stress has a long and rich history in efforts to understand the emergence and perpetuation of psychopathology. Across this history, the field's conceptualization of life stress and its impact has undergone several transformations as theories have progressed from fairly simplistic views to more complex perspectives that acknowledge interactions and transactions among stressful life experiences and multiple vulnerability and protective factors (for reviews, see Grant et al., 2003; Grant et al., 2014). Advances also are reflected in the elucidation of developmentally sensitive models that consider the crucial role of early adversity and salient stage-specific stressors across childhood and adolescence. Accordingly, scholars have made efforts to conceptualize and explore the role of life stress within the context of integrative, dynamic, and developmental frameworks.

In one early conceptualization, Holmes and Rahe (1967) advocated a stimulus-based approach, viewing stress as exposure to disruptive or demanding environmental circumstances, thus emphasizing the objective experience of stress (see also Brown & Harris, 1978). In contrast, Selye (1974) conceptualized stress in terms of external events that elicit certain distress responses, called the general adaptation syndrome. This type of response-based approach is reflected in current neuroscience perspectives that view stress in terms of the type and magnitude of physiological response elicited by an event or circumstance (McEwen & Seeman, 2006). Advocating a transactional approach, Lazarus and Folkman (1984) noted the importance of considering not only environmental events and conditions but also individuals' subjective appraisals of these circumstances (e.g., as harmful, threatening, or challenging). According to this perspective, individual perceptions of events determine their stressfulness. These differing perspectives have pushed the field forward, highlighting distinct yet related aspects of life stress, yet each has been critiqued for focusing on only limited aspects of stressful experiences.

Integrating across these perspectives, Grant and colleagues (2003, 2014) have presented a comprehensive developmentally sensitive stress-based etiological model of psychopathology. Emphasizing the need to distinguish external environmental stressors from internal stress responses, this model defines stressors as "environmental events or chronic conditions that objectively threaten the physical and/or psychological health or well-being of individuals of a particular age in a particular society" (p. 449). In this definition, the term *stressors* serves as a global umbrella incorporating chronic environmental conditions (e.g., ongoing peer rejection), major life events (e.g., death of a parent), and minor life events (e.g., arguing with a friend); although not specified, these stressors also may include normative developmental challenges (e.g., entering into romantic relationships). Objective stressors are believed to undermine biological, psychological, and social processes (i.e., mediators) in ways that heighten risk for psychopathology. This model also elaborates possible characteristics of children and their environments (e.g., age, sex, social support, cognitive or coping styles) that moderate the associations among stressors, mediational

processes, and mental health outcomes. Another proposition focuses on specificity in the association between particular stressors, mediators, moderators, and psychopathology. Finally, the model proposes reciprocal and dynamic influences among stressors, mediators, and moderators that predict the onset and exacerbation of psychopathology. Thus, this framework incorporates both objective conditions and subjective reactions yet distinguishes their etiological status, such that cognitive and emotional appraisals and physiological responses to stress are viewed as potential mechanisms through which objective stressors trigger psychopathology or as moderators that determine the direction and strength of influence of stress on psychopathology.

Beyond the conceptualization of life stress as a proximal contributor to psychopathology, over the past few decades developmental psychopathologists have focused intense attention on the adverse long-term consequences of early social adversity (Boyce & Ellis 2005; Bush & Boyce, 2014; Esposito & Gunnar, 2014). Early adversity has been broadly construed, incorporating experiences such as exposure to socioeconomic disadvantage, parental psychopathology, deprivation, maltreatment, neighborhood violence, insecure attachment, and cumulative lifetime family disruption (for reviews, see Bush & Boyce, 2014; Goodman & Brand, 2009; Goodman & Tully, 2008; Gunnar & Loman, 2011). Although each type of early social adversity may have unique implications for children's development (for some examples, see later sections), common risk processes also have been identified across these experiences in an effort to understand their etiological contribution to future psychopathology.

O'Connor (2003) distinguished two models accounting for individual differences in the long-term impact of early experience. An experience-adaptive or developmental programming model holds that biological systems adapt to environment input, particularly during sensitive periods of development; moreover, this malleability is developmentally constrained such that systems have difficulty readjusting to later changes in the environment. A cumulative effects model holds that early experiences have a long-term impact to the extent that these effects are reinforced or maintained by later events; this model includes both an additive effects variant (the effects of later adversity add to the effects of earlier risks) and an interactive effects variant (the effects of later adversity depend on the history of earlier risks). Stress-sensitization models, discussed earlier, represent one example of this interactive effects variant. According to these models, stressful early experiences are encoded in the brain in the form of memory traces that heighten reactivity of biological stress-response systems, thereby lowering their threshold for reactivity (for a review, see Monroe & Harkness, 2005). Boyce and Ellis' (2005) biological sensitivity to context (BSC) model combines elements of the experience-adaptive and cumulative effects models; specifically, the BSC model holds that early adversity calibrates the stress-response system, such that youth exposed to stressful early social environments show heightened biological sensitivity to later stress. Departing somewhat from other risk models, this sensitivity is thought to exert risk-augmenting effects under subsequent stressful conditions but risk-protective effects under subsequent supportive conditions (Bush & Boyce, 2014).

Refining these stress-based models of psychopathology, contemporary theory and research are aimed toward articulating specific pathways through which risk processes unfold (for reviews, see Esposito & Gunnar, 2014; Goodman & Brand, 2009; Gunnar & Loman, 2011). One line of research, consistent with stress-sensitization and BSC theories, focuses on the idea that a history of prolonged or severe social adversity sensitizes developing brain systems so as to create more pronounced reactivity to stress later in life (for reviews, see Bush & Boyce, 2014; Gunnar & Loman, 2011). Another line of research suggests that early adversity induces risk through exposure to maladaptive parent socialization patterns and stressful interpersonal contexts that weaken youths' developing sense of self, emotion regulation and coping skills, and interpersonal competencies, leaving them vulnerable in the face of future stress or even causing them to generate stressful events and circumstances (for reviews, see Goodman & Tully, 2008; Hammen, 2009; Rudolph et al., 2008).

Developmental Significance and Change. Stress-based theories uniformly emphasize the long-term developmental significance of early social adversity and proximal life stress as instantiated in subsequent biological, cognitive, emotional, and interpersonal risk. However, consistent with a developmental psychopathology perspective, it is vital to consider how stress-linked risk dynamically evolves across the life course in tandem with changes in the occurrence and meaning of particular stressors as well as how early stress intersects with normative developmental tasks and challenges in ways that amplify—or perhaps dampen—earlier risk.

Considerable transformations occur in the nature, role, and consequences of close relationships across development, resulting in changing demands and standards for interpersonal success. Each developmental stage carries new challenges, with the potential to endow satisfaction

from achieving new interpersonal goals (e.g., developing strong friendships during middle childhood) or to induce stress from failing to meet new social demands (e.g., having difficulty balancing connectedness vs. autonomy within parent–child relationships during adolescence). In particular, adolescence often is characterized as a tumultuous period, fraught with novel interpersonal stressors induced by physical-maturational, cognitive-developmental, and social-contextual transitions (Rudolph, 2014). Youth who struggle with these transitions may be at particular risk for interpersonal disruptions that pose a threat for psychopathology. Moreover, developmental changes in relationships may be a particular burden for adolescent girls in light of their stronger interpersonal engagement and sensitivity (for a review, see Rose & Rudolph, 2006). Indeed, research suggests that the transition through adolescence is characterized by a pileup of stressful events and circumstances, especially in the interpersonal domain, with girls showing heightened stress exposure and reactivity compared to boys (e.g., Rudolph & Hammen, 1999; Shih, Eberhardt, Hammen, & Brennan, 2006; for reviews, see Hammen, 2009; Rudolph, 2002). These findings suggest that interpersonal stress-based theories of psychopathology must consider relevant developmental and sex differences in risk over time.

Beyond greater stress exposure, the adverse impact of interpersonal stress may be intensified during adolescence by puberty-linked changes in brain structure and function (for a review, see Dahl, 2004). Contemporary affective and cognitive neuroscience perspectives focus on a growing disjuncture between brain systems involved in the regulation of arousal, motivation, and emotion and those involved in cognitive modulation of behavior (e.g., executive functions that guide judgment and decision making). Specifically, these theories propose an emerging imbalance during puberty reflected in increasing reactivity of sublimbic regions involved in emotion processing (e.g., amygdala, ventral striatum) accompanied by a lag in the maturation of the prefrontal cortex and associated cognitive control processes. This maturational gap is thought to trigger biological sensitivity, emotion dysregulation, risk-taking behavior, and associated risks during adolescence (Dahl & Gunnar, 2009). Thus, heightened stress reactivity may potentiate risk associated with increasing levels of interpersonal stress exposure during this stage. Risk may be most salient in youth exposed to early adversity, who likely enter the adolescent transition with compromised social skills and interpersonal resources (Rudolph, 2009).

Although prevailing interpersonal stress theories of psychopathology focus on this notion that early adversity and escalating interpersonal stress at puberty promote continuity—and perhaps intensification—of maladaptive developmental pathways across adolescence, stress theorists recently are considering possible mechanisms driving discontinuity in risk across development. This perspective is predicated upon the assumption that puberty represents a period of developmental plasticity during which considerable reprogramming occurs in stress-response systems (Dahl, 2004). The adaptive calibration (DelGiudice, Ellis, & Shirtcliff, 2011) or pubertal stress recalibration (Esposito & Gunnar, 2014) hypothesis argues that puberty provides a window of opportunity during which stress-response systems can be recalibrated based on current demands, such that youth who were exposed to early social adversity but then experience supportive, low stress conditions during adolescence may rebound, allowing for protection against psychopathology. Validation of this hypothesis awaits support from rigorous prospective longitudinal research, but it provides a possible explanation for variations in the developmental consequences of early social adversity.

Application to Psychopathology. Exposure to interpersonal stress occupies a prominent position in many developmental psychopathology theories of disorders. The fundamental assumption common across stress-based risk models is that heightened stress exposure overwhelms youths' personal resources and compromises multiple systems of development, thereby precipitating mental health problems. Once again, this line of research highlights the possibility of multifinality (exposure to similar stressors predicts different mental health outcomes) as well as equifinality (exposure to different stressors predicts the same mental health outcome) in youths' developmental trajectories. For the most part, interpersonal stress is incorporated into broader models of psychopathology that implicate diathesis-stress interactions, wherein exposure to stress differentially affects youth depending on prior vulnerabilities (e.g., cognitive biases, emotional deficits) and supports (e.g., risky vs. protective social environments). In the following sections, we focus chiefly on the role of stress itself; the interface between stress and other risks will be described more fully in a later section.

We again present representative examples of relevant models and rely, where possible, on integrative summaries and reviews to cull empirical evidence regarding the role of interpersonal stress in psychopathology. Of note, despite the incredible proliferation of life stress-psychopathology research in youth (over 2000 studies in the past 20 years; Grant et al., 2014), quantitative analyses are not available to estimate the strength of stress-psychopathology linkages. However, in the most comprehensive set of

reviews to date (Grant et al., 2003, 2006; Grant, Compas, Thurm, McMahon, & Gipson, 2004; McMahon, Grant, Compas, Thurm, & Ey, 2003), Grant and colleagues conclude that there is unequivocal support for the prospective contribution of stressors, both cumulative and specific severe stressors (e.g., divorce, poverty), to internalizing psychopathology (e.g., anxiety and depression) and externalizing psychopathology (e.g., aggression and delinquency). Unfortunately, these reviews often do not distinguish specific types of stressors, thereby making it impossible to discern the precise contribution of interpersonal stress to various forms of psychopathology.

Depression Early life stress theories of depression focused on how exposure to adverse life events or circumstances triggers depression onset, persistence, or recurrence (Brown & Harris, 1978). Following this emphasis on the contribution of life stress to depression, research aimed to disentangle symptom-related stress from fateful or independent life events, or events whose occurrence is beyond one's control. This theoretical perspective drove the development of contextual threat (Brown & Harris, 1978) approaches to stress assessment that filtered out individuals' subjective perceptions of threat—which may be biased by depressive symptoms—focusing instead on the objective impact of stress on adjustment. Challenging this traditional view of depressed individuals as passive recipients of experience, Hammen (2006) asserted that understanding the social context of depression requires a consideration of how individuals contribute to stressful environments. Specifically, disorder-induced impairment and stable characteristics of depressed and depression-prone individuals may create stress, which then perpetuates and exacerbates symptoms. This stress-generation process can help explain the continuity and recurrence of depression over time (Rudolph, Flynn, Abaied, Groot, & Thompson, 2009). Although stress exposure and generation can occur within noninterpersonal contexts, life stress theories of depression emphasize the potent role of interpersonal stress.

Collectively, these theories presume that interpersonal stress, conflict, and disruption, particularly stressors that deplete one's self-worth, interfere with the normative acquisition of competencies that emerge in the context of adaptive relationships, such as forming a healthy sense of self and others and learning how to effectively regulate emotions and behavior. Interpersonal stress also can overwhelm youths' coping resources and erode their social networks, creating a sense of helplessness and loneliness. Moreover, interpersonal stress can sensitize biological stress-response systems, thereby heightening reactivity to subsequent stress. These impairments create a vulnerability for depression, which then causes further deterioration in relationships and the generation of more stress (Hammen, 2009; Rudolph et al., 2000, 2008). Thus, consistent with developmental psychopathology principles, interpersonal life stress theories of depression implicate transactional processes through which social disruption and depression become intimately linked within a self-perpetuating cycle over time. Developmental elaborations of these models focus on interpersonal stress as a specific context for the emerging sex difference in depression during adolescence, suggesting that girls are particularly sensitive to disruption in their relationships (Rudolph, 2002, 2009; Rudolph, Hammen, & Daley, 2006; Shih et al., 2006).

A sizeable body of research provides convincing support for life stress as a precursor to depressive symptoms and, to a lesser extent, the onset of depressive disorders in youth. Much of this research relies on composite measures of cumulative events across multiple domains, making it difficult to determine the specific role of interpersonal stress. However, individual studies do indicate that chronic interpersonal stress, cumulative interpersonal life events, and specific types of interpersonal events prospectively predict depression. A growing body of evidence also supports the notion that depressive symptoms predict the generation of interpersonal stress (for reviews, see Hammen, 2009; Rudolph et al., 2006). In their broad review, Grant and colleagues (2006) generally found stronger associations between cumulative or specific life stressors and internalizing symptoms in girls than in boys, qualified some by the type of stressor. Moreover, one recent study indicated that self-generated interpersonal (but not noninterpersonal) stress accounted for the continuity of depression in girls but not boys, supporting transactional interpersonal life stress models of depression and the sex difference therein (Rudolph et al., 2009). Confirming the importance of developmentally sensitive life-stress models, research also reveals an intensification of the interpersonal life stress-depression link at puberty. In particular, early maturation interacts with family and peer stress to predict subsequent depression, and depression interacts with early maturation to predict subsequent interpersonal stress generation (for a review, see Rudolph, 2014). Finally, research supports theoretical models asserting that exposure to early social adversity heightens risk for subsequent youth depression, often through stress-amplification or stress-sensitization processes (for reviews, see Goodman & Brand, 2009; Hammen, 2009; Hammen et al., 2014).

Anxiety Exposure to stressors also is an integral component of many etiological theories of anxiety. Early

perspectives linking stressors with anxiety emerged from classical conditioning theories suggesting anxiety resulted from pairing of a neutral stimulus with a traumatic event. Attempting to explain individual differences in the presence of a conditioned stimulus in individuals with anxiety, more contemporary accounts consider the role of preexisting vulnerabilities, previous learning experiences and stressors, and poststressor experiences (Murray, Creswell, & Cooper, 2009).

Barlow and colleagues (Albano et al., 2003) presented a multifaceted model that emphasizes the crucial role of life stressors as setting into motion a causal chain eventuating in anxiety. It is believed that early exposure to stress fosters changes in neural systems underlying stress responses and engenders a psychological vulnerability characterized by a diminished sense of control, which in turn drives anxiety. The model does not specify whether stressors occurring within the interpersonal domain are particularly relevant to anxiety; rather, the focus is on early stressful events or conditions that predispose children to acquiring a cognitive template characterized by a weakened sense of predictability, control, or mastery. Of note, this model proposes that the actual nature of life events becomes less influential across development, as this cognitive template strengthens subjective appraisals of stress.

Whisman and Beach (2010) provided a framework for understanding the specific role of early interpersonal stress in the development of anxiety. They propose that stressors viewed as being intentionally inflicted are more likely to undermine mental health, thus implicating the salient role of interpersonal stressors. Furthermore, they suggest early severe and cumulative exposure to interpersonal stressors will sensitize individuals to subsequent stress, thereby heightening risk for anxiety, although they allow for the possibility that moderate levels of stress may induce resilience. Similar to interpersonal life stress theories of depression, this framework integrates the ideas that (1) interpersonal stressors pose particular risk for anxiety in girls compared to boys (see also Davila, La Greca, Starr, & Landoll, 2010); (2) sensitivity to interpersonal stressors increases during developmentally salient life transitions, such as puberty; and (3) anxiety symptoms contribute to the generation of future interpersonal stress (e.g., through avoidance, missed opportunities for socialization, and consequent failure to develop adequate social skills; Davila et al., 2010), resulting in a self-sustaining cycle of symptoms and stress-inducing behavior.

Supporting interpersonal stress models of anxiety, both early social adversity and recent stressors predict anxiety symptoms and disorders in youth, with some specificity for anxiety versus depression (for reviews, see Davila et al., 2010; Grant et al., 2014). As noted earlier, some evidence supports stronger links between stress and internalizing symptoms, broadly construed, in girls than in boys (Grant et al., 2006). Although little research implicates specific types of interpersonal stressors, there is some evidence that threat events (e.g., threat of caregiver loss, physical jeopardy, psychological challenge) are uniquely associated with youth anxiety compared to depression (Eley & Stevenson, 2000). Finally, preliminary evidence supports stress-generation processes in anxiety (Murray et al., 2009; Whisman & Beach, 2010).

Externalizing Psychopathology The frustration–aggression hypothesis (Dollard, Doob, Miller, Mowrer, & Sears, 1939) postulates that aggression emerges from emotional arousal elicited by aversive events that thwart one's desired goal attainment. Although aspects of this hypothesis have undergone significant critique, the idea that exposure to aversive or stressful events induces aggression (and other types of externalizing psychopathology) has remained a part of many theoretical models. The assumption is that stress exposure leads to arousal and negative affect (e.g., anger, hostility), which are expressed in the form of aggressive and delinquent behavior.

Integrating aspects of the frustration–aggression hypothesis, many contemporary stress-based accounts of externalizing psychopathology represent variants of strain theory. The core assumption of strain theory is that youth who live in aversive environments (e.g., those characterized by poverty, neighborhood disadvantage, and associated chronic stressors) are unable to achieve valued goals via legitimate channels and, therefore, turn to delinquency and crime (Agnew, 1985). Responding to critiques of this theory and some empirical failures to support its assumptions, Agnew (1985) proposed a revised strain theory, which proposes that youth who are embedded in aversive social environments become frustrated not only in reaction to the blockage of goal-seeking behavior but also in reaction to the blockage of pain-avoidance behavior. That is, youth often have no legitimate options for escaping from stressful social environments (e.g., parental rejection; teacher conflict), resulting in aggressive or illegal escape attempts (e.g., fighting with peers to reduce harassment; running away to escape stressful home environments) or in anger-based aggression and delinquency. The former would incite proactive, instrumental antisocial behavior and the latter would incite reactive, emotionally driven antisocial behavior. The likelihood of social strain contributing to antisocial behavior would be contingent on other factors, such as youths' beliefs about delinquency, integration into deviant peer groups, and level of social control (internalization of conventional norms and values).

Some effort has been made to elucidate specific types of social stressors most likely to predict externalizing psychopathology. Agnew (2001) suggested several broad characteristics of strain that enhance its likelihood of promoting delinquency and criminality; these include strains that (1) are perceived as unjust (which induces anger and a desire for revenge, inhibits guilt, and impedes adaptive coping); (2) are perceived as severe in magnitude (which interferes with adaptive coping, attenuates its likelihood of success, and increases the perceived cost of the strain); (3) are associated with low social control (which reduces the perceived cost of delinquency and one's ability to engage in adaptive coping); and (4) create pressure or incentives to engage in criminal coping (e.g., exposure to others who model or reinforce crime or to conditions that diminish the utility of adaptive coping and maximize the benefits of aggression and delinquency; see also Attar, Guerra, & Tolan, 1994). According to Agnew (2001), some interpersonal strains with these characteristics include parental rejection, harsh discipline, peer maltreatment, and other forms of victimization and discrimination.

Similar to interpersonal stress theories of depression and anxiety, strain theory has been applied to understanding sex differences in stress and externalizing psychopathology. Briefly, Broidy and Agnew (1997) proposed that males may show higher rates of delinquency and criminality than females in reaction to strain because (1) they experience more of the types of strain associated with violence and delinquency; (2) although both males and females respond to strain with anger, females experience the associated emotions of depression, guilt, and anxiety, which inhibit aggressive reactions; and (3) anger more likely provokes aggression and delinquency in males because of their typical coping strategies, weaker affiliative tendencies, involvement in peer group networks that promote physical confrontation and risk taking, and experience of fewer societal inhibitions against aggression. Focusing on life stress more generally, Leadbeater and colleagues (1995) proposed that adolescents with an individualistic orientation (who are sensitive to criticism), which is more characteristic of boys than girls, are more likely to respond to stress—particularly stress that threatens the self—with externalizing psychopathology in order to maintain personal power and deflect perceived criticism.

Consistent with stress-based theories, exposure to a variety of social stressors (e.g., neighborhood disadvantage and violence, aversive family and school environments, cumulative life events) predicts externalizing psychopathology (Attar et al., 1994; for reviews, see Agnew, 1985, 2001; Grant et al., 2006); consistent with strain theory, some of these effects are accounted for by heightened levels of anger (Agnew, 1985). There is some evidence supporting links between certain types of strain and externalizing psychopathology (for a review, see Agnew, 2001) as well as stronger links between stress and externalizing psychopathology in boys than in girls (for a review, see Grant et al., 2006; cf. Attar et al., 1994; Hoffmann & Su, 1997), although more research of this type is needed.

Stressor-Specific Theories

Although some theoretical models focus on cumulative life stress exposure, others postulate how specific severe interpersonal stressors heighten risk for psychopathology. These conceptualizations often integrate other interpersonal models of psychopathology to explain how stress exposure exerts long-term toxic consequences on mental health. For example, theoretical models often assert that specific life stressors contribute to psychopathology via disruptions in family processes (e.g., insecure attachment, poor parenting, family conflict) or peer processes (e.g., affiliation with deviant peers, disruption in social networks). Below we describe a few such models; this summary is not exhaustive but rather provides representative examples of theories concerning how specific stressors increase the likelihood of multiple forms of psychopathology within an interpersonal context.

Family Adversity. Some interpersonal stressors impinge directly upon youth by threatening parent–child bonds and family relationships; others exert indirect influences on youth by limiting family resources, creating parenting strain, and compromising parents' mental health in ways that impair their ability to act as support systems for youth. Regardless of the specific form, family adversity exposes youth to punitive, stressful, or unpredictable family environments. In the following sections we discuss four exemplars of such stressors that have received significant attention in interpersonal theories of psychopathology.

Socioeconomic Risk Several related theoretical models contend that exposure to poverty heightens risk for psychopathology through interpersonal mechanisms (e.g., Conger, Ge, Elder, Lorenz, & Simons, 1994; Wadsworth, Raviv, Santiago, & Etter, 2011). These models share the idea that economic strain compromises family health, resulting in maladaptive parenting (e.g., harshness, rejection, inconsistent discipline), parental depression, and family conflict; this family disruption then puts youth at risk for multiple forms of psychopathology. In a meta-analytic review of this pathway, Grant et al. (2003) provided evidence for the validity of family process models of socioeconomic risk. In particular, poverty predicted poor parenting, which predicted heightened internalizing

and externalizing symptoms over time. The overall model fit the data somewhat better for girls than for boys; moreover, the association between poverty and poor parenting was stronger in boys than in girls, whereas the association between poor parenting and internalizing symptoms was stronger in girls than in boys. More recent work focuses on understanding how some families and youth are resilient in the face of economic strain. For example, Wadworth and colleagues (2011) proposed a model wherein effective coping and stress reduction mitigate the adverse effects of economic strain on family functioning, thereby reducing long-term risk for psychopathology. Overall, this line of theory and research provides a global perspective on risk for psychopathology—particularly anxiety, depressive, and externalizing symptoms—arising from poverty and ensuing family disruption, with little indication of circumstances accounting for differential risk for specific types of disorder.

Maltreatment Exposure to maltreatment is a traumatic form of family adversity that can forebode future psychopathology. Cicchetti and Banny (2014) proposed an ecological-transactional model in which maltreatment is viewed as a pathogenic relational environment that compromises the achievement of key developmental milestones, propelling children along a pathway of risk for repeated developmental failures and the emergence of psychopathology. This model allows for *multifinality* in the developmental trajectories of maltreated youth, with some moving toward compromised development and psychopathology and others toward healthy adaptation. Perturbations in diverse stage-salient developmental processes are implicated as potential paths through which maltreatment instills risk: (1) maltreatment fosters an aberrant emotional environment in the context of the parent–child relationship; early exposure to this environment compromises the emergence of skills for differentiating and modulating emotions, thus resulting in deviant emotional expression (e.g., excessive negative or blunted affect), attention (e.g., a bias toward angry faces), and arousal processes (e.g., under- or over-controlled); (2) exposure to insensitive and hostile care provokes the emergence of insecure (particularly disorganized) attachment and negative internal working models; (3) maltreated children show deviant self-system development, reflected in negative (for neglected) or grandiose (for abused) self-representations, low self-esteem, and dissociative symptoms; (4) maladaptive interactional patterns developed within a maltreating relationship create ongoing interpersonal problems within the peer group, such as aggression, victimization, and poor quality friendships; (5) certain subtypes of maltreatment foster deviant memory processes (e.g., defensive processes, overgeneral autobiographical memory); and (6) chronic physiological activation resulting from maltreatment disrupts biological systems regulating stress reactivity, resulting in allostatic overload. Collectively, disruptions across multiple domains create a cascade of developmental challenges that potentiate long-term liability for multiple forms of psychopathology, including mood and anxiety disorders, dissociation, suicidal behavior, substance use, antisocial behavior, psychosis, and personality pathology (Cicchetti & Banny, 2014). Of importance, this model emphasizes that maltreatment represents only a probabilistic risk for psychopathology that is contingent upon genetic liability.

Presenting an integrative developmental model specifically linking early maltreatment with depression, Harkness and Lumley (2009) stipulate that exposure to abuse and neglect promotes the development of core negative belief systems (e.g., negative attributional style, maladaptive cognitive schema) and dysregulation of the HPA axis (hippocampal atrophy and cortisol hypersecretion). These processes interact and stabilize throughout adolescence, coalescing into rigid structures that prime sensitivity to future stress and even cause the generation of stress, thereby heightening risk for depression. Although accumulating research supports parts of this model (e.g., effects of maltreatment on cognitive and biological vulnerability; stress sensitization in maltreated youth; for a review, see Harkness & Lumley, 2009), the model has not yet been tested in full.

Family Conflict Focusing on family conflict as a severe stressor, Davies and Sturge-Apple (2014) proposed that repeated exposure to interparental conflict or hostility in parent–child relationships sensitizes children to sources of threat, which compromises their sense of security and puts them at risk for psychopathology. In the face of these threats, children may show self-protective behaviors such as triangulation or alliance formation, avoidance, and hypervigilance to threat cues, all of which are developmental precursors to psychopathology.

The process of triangulation in the context of interparental conflict has received much attention as a stressor. Fosco and Grych (2008) reviewed three main forms this triangulation can take. First, children may become involved in their parents' disputes to try to help resolve them. Second, children may form an alliance with one parent against the other. Third, children may misbehave to direct parents' attention toward them and away from the marital discord.

Becoming involved in interparental conflict has the potential to undermine children's adjustment because forming an alliance with one parent might reduce their access to support from the other parent, redirecting parents' anger toward themselves might increase children's emotional distress, and behavior problems themselves might become habitual as children try to keep parents' focus away from their marital problems. Many aspects of these theoretical models of family and interparental conflict as risk factors for psychopathology are bolstered by empirical support (for a review, see Davies & Sturge-Apple, 2014).

Early Deprivation One of the most profound interpersonal stressors experienced by youth is exposure to extreme deprivation in the context of severely inadequate caregiving environments. Spurred by a surge in children exposed to global deprivation within institutional care settings abroad, scientists have scrutinized the implications of this early experience for the development of psychopathology (for a review, see Esposito & Gunnar, 2014). This line of research takes advantage of a natural experiment, in that many youth exposed to early deprivation typically enter into supportive environments (through adoption) during infancy or early childhood, affording the opportunity to ascertain the enduring effects of early social adversity and to better understand processes of recovery and resilience.

Esposito and Gunnar (2014) illustrated two theoretical perspectives on the impact of early deprivation. Theories of experience-expectant development suggest that stimulus depletion associated with deprivation interferes with neural development during sensitive periods, creating delays or deficits in cognitive, emotional, and motor development. A life stress perspective suggests that early deprivation and the accompanying absence of caregivers to provide regulatory input serves as a chronic stressor that causes dysregulation in the HPA axis, stress-related neuropeptides, and neurotransmitters or even creates epigenetic changes in the stress-regulatory systems that manage threat and challenge. These two perspectives are not mutually exclusive and may account for different adverse effects of early deprivation.

More specifically, characteristics of early deprivation (e.g., lack of environmental stimulation, absence of a close caregiving relationship) are thought to result in a failure to succeed on salient development tasks such as establishing a secure attachment, an advanced theory of mind, and cognitive and emotional regulatory skills (e.g., executive function, attentional control) during earlier childhood. Deprivation also predicts compromised biological functioning (e.g., impaired cellular growth and repair; growth delays; HPA axis dysregulation; delayed neural maturation; abnormalities in brain structure and connectivity). Highlighting the importance of a developmental perspective, Esposito and Gunnar (2014) suggest that deprivation-induced impairment may interact with heightened challenges in adolescence to forecast emerging psychopathology during this stage, yet adolescence also may represent a period of opportunity during which biological systems rebound, and risk for psychopathology decreases in the context of a supportive environment. Despite the compelling findings documenting adverse sequelae of early deprivation, few studies explicitly examine whether these processes mediate between deprivation and subsequent psychopathology or whether adolescence brings heightened risk or resilience.

Peer Adversity. Challenging conventional wisdom suggesting that exposure to adversity within the peer context represents a normative part of growing up, theoretical perspectives increasingly view these experiences as traumatic stressors with the potential to set youth upon trajectories of risk for psychopathology. Indeed, many forms of peer adversity share characteristics of family adversity (e.g., exposure to negative self-referent feedback, demeaning treatment, and even emotional and physical abuse) that can jeopardize the achievement of key developmental tasks and heighten vulnerability across multiple systems of development.

Peer Rejection Exposure to peer rejection can be viewed as a developmentally salient interpersonal stressor that threatens youths' well-being by compromising their sense of self (La Greca et al., 2011; Prinstein & Aikens, 2004), priming cognitive biases (Dodge et al., 2003) and emotion dysregulation (Bierman & Wargo, 1995), and forcing youth outside of the mainstream peer group (Dishion, 2014), thereby increasing their likelihood of developing psychopathology (Choukas-Bradley & Prinstein, 2014; Parker et al., 2006). Consistent with vulnerability models, it has been proposed that exposure to peer rejection will predict depressive symptoms in youth with but not without predisposing cognitive vulnerabilities (Prinstein & Aikins, 2004). In the context of problem behavior (externalizing psychopathology, substance use, risky sexual behavior), it has been proposed that early aggression will predict subsequent symptoms in youth exposed to low social preference (peer rejection) but not high social preference (peer acceptance) (Prinstein & La Greca, 2004). Consistent with stress-generation models, peer rejection also has been conceptualized as a potential consequence of depressive symptoms (Agoston & Rudolph, 2013; Kochel, Ladd, & Rudolph, 2012) and aggression (Dishion, 2014). This perspective highlights the continuous transactions between interpersonal stressors and psychopathology.

More broadly, contemporary theories consider how social rejection gets under the skin (e.g., Slavich, Donovan, Epel, & Kemeny, 2010) to heighten risk for psychopathology, processes that will be explored further.

Peer Victimization Conceptualizing peer victimization within a life stress perspective, Rudolph and colleagues (Troop-Gordon, Rudolph, & Sugimura, 2015; Troop-Gordon, Rudolph, Sugimura, & Little, 2015) proposed a model wherein victimization serves as a form of early social adversity that interferes with the normative development of self-regulatory processes in ways that heighten risk for psychopathology. Typically, peers help shape emerging self-regulatory abilities by modeling and providing feedback about effective coping and acting as support systems that encourage effective self-regulation. Because victimized youth are marginalized from the mainstream peer group, they have limited opportunity for positive socialization; moreover, their coping resources may become overwhelmed, impairing their ability to manage reactions to social stress. Youth who anticipate aggression or humiliation from peers due to a history of victimization also may show heightened vigilance and consequent biological reactivity to social threat. According to this model, therefore, early exposure to peer victimization will predict heightened stress reactivity over time, as reflected in involuntary, dysregulated cognitive, emotional, behavioral, and physiological responses to social challenges. This heightened stress reactivity, in turn, enhances risk for psychopathology.

Preliminary research supports this model. Specifically, early exposure to peer victimization and increasing victimization over time predict maladaptive growth patterns of involuntary engagement (e.g., rumination, impulsive action) and disengagement (e.g., emotional numbing, escape) responses to stress over time (Troop-Gordon et al., 2015). Moreover, involuntary engagement and disengagement responses to stress mediate the prospective contribution of peer victimization to subsequent depressive symptoms (Troop-Gordon et al., 2015). Research also links victimization to heightened biological reactivity in response to social challenge (Kliewer, Dibble, Goodman, & Sullivan, 2012). More generally, research supports a prospective contribution of victimization to multiple forms of psychopathology, including general and social anxiety, depression, and externalizing symptoms (Davila et al., 2010; Rudolph, Troop-Gordon, Hessel, & Schmidt, 2011). Consistent with stress-generation models, internalizing and externalizing psychopathology also contribute to subsequent peer victimization (Davila et al., 2010; Rudolph, Lansford et al., 2014).

Peer Exclusion Persistent exclusion from the peer group also has been viewed as an interpersonal stressor that heightens risk for psychopathology (Davila et al., 2010; Gazelle & Rudolph, 2004). Exclusion may occur through direct actions (e.g., refusing a child's bid to participate in group activities) or through indirect actions (e.g., failing to involve a child in the peer group). Drawing from diathesis-stress models of psychopathology, Gazelle and Rudolph (2004) suggested that exposure to peer exclusion may exacerbate risk associated with a tendency toward anxious solitude, characterized by shy, verbally inhibited, and solitary behavior among familiar peers (Rubin et al., 2009). Specifically, they reasoned that when the beliefs of anxious solitary children (e.g., fears about negative evaluation or maltreatment) are confirmed through peer exclusion, they will progress from worrying about the possible occurrence of negative peer events and their ability to respond effectively (a risk for anxiety symptoms) to being certain about the occurrence of negative peer events and convinced of their inability to cope (a risk for depressive symptoms). In support of this theory, a prospective study revealed that children who were both anxious solitary and excluded reported higher stable levels (for girls) or increasing levels (for boys) of depressive symptoms over time. Peer exclusion also has been implicated in social anxiety (Davila et al., 2010). Thus, peer exclusion represents a specific interpersonal stressor that can pose a risk for internalizing psychopathology, particularly in youth with a heightened sensitivity to exclusion.

Romantic Relationship Stressors Romantic involvement represents a normative process with the potential to provide opportunities that enhance well-being or to present challenges that undermine healthy development. Although increasing involvement in romantic relationships is typical across mid- to late adolescence, emerging theory and research suggest this involvement also heightens risk for psychopathology. Dating and romantic relationships can create stressful experiences and events (e.g., harassment, breakups, conflict) that threaten youths' mental health. However, several theoretical models propose that romantic involvement even in the absence of specific stressors can have adverse effects (for a review, see Davila, 2008).

According to a normative trajectory model (Davila, 2008), youth who become involved in dating and romance during early adolescence (considered to be early and thus off-time) are failing to conform to developmental norms, which compromises their adjustment. According to an attention impairment model (Joyner & Udry, 2000), romantic involvement deflects attention from other key

developmental tasks (e.g., attaining academic success, sustaining strong friendships and family relationships), which has adverse mental health effects. According to a stress and coping model (Davila, 2008), novel activities and experiences (e.g., initiation of sexual behavior, development of intimacy) and intense, novel emotions (e.g., romantic love, passion, sexual attraction) emerging within romantic relationships may pose challenges for youth, particularly those with inadequate coping resources and other vulnerabilities. Theoretical models of puberty and psychopathology further propose that premature entrance into dating and romantic relationships, especially for early-maturing girls, paves the way for affiliation with older and more deviant peers, which facilitates the onset or progression of antisocial behavior and substance use (for a review, see Rudolph, 2014).

Supporting models of romantic risk, romantic stressors, attraction, involvement, and activities (e.g., flirting, dating, sexual activity) predict symptoms of depression (for a review, see Davila, 2008). Contrary to a purely normative trajectory model, this risk occurs not only in early adolescence but also at older ages. However, romantic involvement and stress do help to account for the association between early pubertal timing and multiple forms of psychopathology, including depression and externalizing psychopathology (for a review, see Rudolph, 2014). Poor-quality romantic relationships also are associated with higher levels of anxiety (for a review, see Davila et al., 2010). Reflecting a transactional process, psychopathology, such as depression, also predicts subsequent disruption within romantic relationships (Daley & Hammen, 2002).

Directions for Future Research on Stress-Based Theories

Significant empirical advances provide compelling evidence for the prospective contribution of interpersonal stressors to psychopathology. This research documents the adverse effects of both cumulative stressors and specific adverse life events, including early as well as more proximal experiences. The field also has progressed in its understanding of personal and contextual characteristics that amplify or dampen stress reactivity. Yet, this line of research still provides a surprisingly broad—and often atheoretical—perspective. Of particular interest here is whether stressors within interpersonal relationships serve as robust predictors of specific forms of psychopathology and, if so, why and for whom?

Despite recent progress (Grant et al., 2014), there is a dearth of conceptually driven research examining specific stressor-psychopathology linkages (McMahon et al., 2003), making it difficult to determine the particular contribution of interpersonal stressors. Progress on this front will require building and testing more sophisticated theoretical models to explain why certain stressors heighten risk for certain disorders. Addressing this issue may be facilitated by considering the pathways through which interpersonal stressors exert their effects as well as characteristics of youth and their environments that determine specific adverse—or even beneficial—consequences of stress (Grant et al., 2006). For example, interpersonal stressors that threaten one's sense of control (e.g., parental divorce) may heighten risk for anxiety; those that deplete one's self-worth (e.g., social rejection) may heighten risk for depression; and those that threaten one's social status (e.g., peer victimization) may heighten risk for externalizing psychopathology. However, the picture is likely more complicated given that individual differences in the mental health consequences of interpersonal stressors undoubtedly depend on personal characteristics such as genetic liability, temperament, or cognitive style as well as environment contexts, such as family or peer support. Thus, advances in the field will require considering how particular stressors contribute to particular types of psychopathology through particular pathways in particular youth under particular circumstances at particular points in development.

Reflecting this approach, interpersonal life stress theories of depression, perhaps the most well-developed and well-tested life stress theories, propose a detailed account concerning how relationship disruptions heighten vulnerability to depression and why these effects may be particularly robust in certain youth (e.g., girls, those with heightened investment in relationships) at certain stages (e.g., adolescent transition) as well as the processes through which depression and associated characteristics contribute to subsequent interpersonal stress (for reviews, see Hammen, 2009; Rudolph, 2009). The field would benefit from the articulation of similar conceptual models guiding assertions about the contribution of interpersonal stressors to other forms of psychopathology. Rigorous prospective and multiwave research designs then will be needed to systematically test these models, including explicit exploration of the pathways through which early social adversity and proximal interpersonal stressors are translated into long-term risk. This research would be aided by systematic quantitative summaries of the field. Future research also will need to take a developmentally sensitive approach that considers whether the adverse mental health consequences of stressors emerge, intensify, or even subside at certain life stages as well as when and how sensitivity to

stress stemming from early adversity represents an asset that confers benefits for development; this research can take advantage of exciting developments in neuroscience that provide insight into how stress exposure interfaces with normative changes in brain development to trigger psychopathology. Finally, interpersonal stress theory and research would benefit from a careful consideration of how early and recent stressors intersect with other domains of risk or resilience, as embodied in various theoretical models (e.g., stress amplification, plasticity, stress sensitization, stress inoculation), to predict psychopathology or even positive youth development.

INTERSECTION BETWEEN INTERPERSONAL THEORIES AND ALTERNATE THEORIES OF PSYCHOPATHOLOGY

Considering how interpersonal vulnerability is linked to other domains of risk (genetic, biological, cognitive, and contextual) can advance the field's understanding of multifinality in developmental pathways as well as clarify the processes through which interpersonal vulnerability contributes to psychopathology. Although our discussion of individual theories inevitably alluded to both moderators and mediators of the consequences of interpersonal experiences, this section provides a more integrative summary of key theories.

Moderators of the Impact of Interpersonal Relationships on Psychopathology

As reflected in our previous discussions, many interpersonal theories form the basis for predicting that interpersonal disruptions can foster diverse forms of psychopathology. In some cases, predictions about specific outcomes may lie in distinguishing particular dimensions of risk (e.g., overprotective parenting that elicits heightened vigilance vs. rejecting parenting that undermines self-worth). In other cases, it is difficult to predict the precise outcomes. To understand individual differences in emerging risk, it is therefore necessary to consider which youth under which conditions will show which forms of psychopathology (or resilience). Throughout the description of individual theories, we mention such possibilities. Here we briefly describe two levels of moderating factors—the molecular (genes and their expression) and the molar (culture and its expression)—that may determine how interpersonal risk is translated into particular outcomes.

Molecular-Level Moderators—Genes and Their Expression

At the molecular level, genes may moderate the contribution of interpersonal environments to psychopathology, conforming to a vulnerability model (genes heighten sensitivity at high levels of interpersonal risk), plasticity model (genes make youth more susceptible to both positive and adverse interpersonal environments), stress-sensitization model (genes sensitize youth such that they require lower levels of interpersonal risk to express psychopathology), or stress-inoculation model (genes bolster resilient outcomes in the face of stress). Identifying specific genetic markers of risk for psychopathology has been a subject of great debate; regardless of the empirical yield of this approach, it reveals little about the processes involved in the development of disorders. Contemporary theoretical models are therefore turning to a focus on endophenotypes—or intermediate level biological, neural, or psychological characteristics—through which genetic risk is translated into psychopathology.

As one example, a polymorphism in the serotonin transporter gene, which moderates the impact of interpersonal risk (e.g., family and peer maltreatment and stress) on depression (Benjet, Thompson, & Gotlib, 2010; Cicchetti, Rogosch, & Sturge-Apple, 2007) and aggression (Brendgen et al., 2008), also is associated with cognitive risk (e.g., biased information processing; Beevers, Wells, Ellis, & McGeary, 2009), biological risk (e.g., HPA reactivity; Gotlib, Joormann, Minor, & Hallmayer, 2008), and individual differences in temperament (e.g., negative emotionality; Pauli-Pott, Friedl, Hinney, & Hebebrand, 2009); these endophenotypes in turn directly moderate the contribution of interpersonal risk to psychopathology (Brendgen, Wanner, Morin, & Vitaro, 2005; Rudolph, Troop-Gordon, & Granger, 2011; Sugimura & Rudolph, 2012). Moreover, there is some tantalizing indication of plasticity genes, which account for differential susceptibility to both adverse and positive environments, although more evidence is needed (Rutter, 2014). Scientists also have identified both genetic variability and specific neural profiles that heighten susceptibility or resistance to peer influence, either amplifying or dampening risk for psychopathology (Brechwald & Prinstein, 2011).

Essentially, genes and their expression can influence how individuals encode, interpret, and react to interpersonal experiences, thereby altering their impact on development. Comprehensive interpersonal theories of psychopathology therefore increasingly consider genetic variations—and perhaps more importantly, their accompanying endophenotypic implications—in how interpersonal adversity is translated into risk for psychopathology.

Molar-Level Moderators—Culture and Its Expression

At the other extreme, broad contextual features of individuals' environments may moderate the association between interpersonal factors and psychopathology by determining the meaning attributed to particular social interactions and relationships. Culture shapes individuals' expectations regarding the normativeness of particular experiences. Attribution theory (Dodge, 2006) posits that individuals' interpretations of behavior are dependent on how frequent the behavior is within a culture as well as a culture's relevant laws, customs, and ideology. Individuals who perceive themselves as experiencing non-normative compared to normative relationships are more likely to personalize an attribution about the experience, thereby heightening their risk for psychopathology (Lansford et al., 2005).

Bornstein (1995) proposed a model differentiating the forms of parenting (i.e., specific behaviors of parents toward children) and the functions of parenting (i.e., the meaning imparted to children). On the one hand, a given form of parenting can serve different functions depending on the cultural context (e.g., parents' derogatory comments about a child may convey hostility in most cultures but love in cultures where they are viewed as protective; DeLoache & Gottlieb, 2000). On the other hand, different forms of parenting can serve the same function (e.g., parents may use direct, such as physical affection and praise, vs. indirect, such as food preparation, behaviors to convey warmth; Bornstein, 1995). Thus, the meaning of particular parent–child interactions and their implications for children's development depend on the cultural context.

In part, cultural meanings are dependent on overarching goals of individuals within the cultural group (Pomerantz & Wang, 2009). For example, despite the documented association between authoritative parenting and optimal development, authoritarian parenting may be more adaptive for children in some cultural groups. Although authoritarian parenting is associated with European American children's fearful behavior, it is associated with African American girls' assertiveness (Baumrind, 1972). Grusec, Rudy, and Martini (1997) theorized that in collectivist cultural groups, in which the needs of the group are given primacy over individual needs, authoritarian parenting may be more adaptive. In such cultural groups, authoritarian parenting is associated with less negative parental affect and cognition than in individualist cultural groups, suggesting that the association between parenting style and children's adjustment depends on the larger cultural context in which families are situated (Rudy & Grusec, 2006).

Similar principles apply to understanding the impact of cultural norms and values on peer-psychopathology linkages. For example, shyness and inhibition relate to psychopathology in Western cultures but to positive indicators of adjustment in China (for a review, see Chen et al., 2014). The conceptual model invoked to explain these differences proposes that the consequences of particular social behaviors depend on how those behaviors fit into patterns that are positively valued within a cultural context. In China, where children's dependence, inhibition, and self-restraint are valued, a child who behaves in a shy or sensitive manner will be regarded more positively than would such a child in a Western culture that values independence and self-expression; in turn, children will be less likely to proceed along a pathway to psychopathology in a cultural context that is consistent with their exhibited behaviors. Of interest, as China has become more Westernized, these cultural differences have diminished (Chen et al., 2014).

Mediators of the Impact of Interpersonal Relationships on Psychopathology

Although the field has witnessed enormous strides in documenting the insidious effects of interpersonal adversity on psychopathology, considerably less is known about how or why this process occurs—that is, the oft-cited question of How do social experiences get under the skin? Most interpersonal theories of psychopathology incorporate ideas about candidate pathways through which social disruption creates risk for psychopathology. Specific pathways are discussed as relevant throughout earlier sections of the chapter; in this section we highlight some of the common themes on which these theories converge.

Biological Pathways

As discussed earlier, development programming theories propose that biological systems adapt to environmental demands, resulting in potentially enduring changes in brain organization (Boyce & Ellis, 2005; O'Connor, 2003). Although potentially adaptive in the short-term, through the process of entraining (Boyce & Ellis, 2005) altered biological systems may constrain possible future developmental pathways followed by youth exposed to early stress, thereby launching them onto trajectories of psychopathology. A notable trend in the field is to explore this biological embedding of experience as a risk mechanism (Bush & Boyce, 2014; Rutter, 2014).

Broadly, many contemporary theories share in common the notion that severe or chronic exposure to social

adversity—including insecure attachment, parent psychopathology, toxic family environments, parent and peer maltreatment, and early social deprivation—taxes physiological systems (e.g., HPA axis, autonomic nervous system, immune system) involved in maintaining homeostasis, thereby intensifying or attenuating their sensitivity. These potentially enduring changes in biological systems underpinning emotion regulation, stress reactivity, and cognitive self-regulation can eventuate in psychopathology (for reviews, see Cicchetti & Rogosch, 2012; Davies & Sturge-Apple, 2014; Esposito & Gunnar, 2014; Goodman & Brand, 2009; Pollak, 2008). Indeed, the recent explosion of theory and research linking social experiences with biological processes has spawned the newly emerging field of social affective neuroscience. Likewise, the field of epigenetics is beginning to unravel how interpersonal experiences guide individual differences in the biological and phenotypic expression (or silencing) of genes (Meaney, 2010).

As one example, social pain theory (Eisenberger, 2012) suggests intriguing possibilities for one biological pathway through which interpersonal adversity is internalized as risk for psychopathology. Building on the idea that social bonding and belonging serve a vital evolutionary role in human well-being, social pain theory suggests that threats to these social needs trigger activation in the same neural circuitry as that underlying physical pain. Supporting this theory, experimental exposure to social injury (e.g., loss, exclusion, rejection, negative social evaluation) activates the dorsal anterior cingulate cortex (dACC) and anterior insula, areas implicated in the affective component of physical pain. Suggesting the importance of individual differences in social orientation, perhaps shaped by past experience, these effects are heightened for individuals with high rejection sensitivity and an anxious attachment. A complementary line of research reveals that the experience of being liked by others activates neural regions involved in reward motivation (Davey, Allen, Harrison, Dwyer, & Yucel, 2010). Moreover, individuals who report feeling more rejected in their everyday social interactions show more social pain (Eisenberger, Gable, & Lieberman, 2007) whereas a history of engagement in positive social experiences protects against social pain (Masten et al., 2010). Collectively, this research suggests that stressful or supportive interpersonal experiences can be instantiated in specific patterns of neural function, which can confer risk for, or protection against, psychopathology. Contemporary theories also suggest social rejection can lead to activation of stress–response systems (HPA and sympathetic-adrenal-medullary axis) and a pattern of pro-inflammatory processes that heighten risk for psychopathology (Slavich et al., 2010), providing promising leads for future research.

Building on the historical work of Harlow (Harlow & Zimmerman, 1959), another fascinating line of research focuses on meaningful differences in the biological profiles of nonhuman primates reared under adverse social conditions (i.e., those that threaten healthy attachment, such as being reared by mothers who are under stress, abusive/rejecting mothers, or peer age-mates). Monkeys raised under these conditions demonstrate dysregulation of the HPA axis (both heightened and blunted reactivity), atypical patterns of neurotransmitter metabolism and cerebral blood flow, and differences in growth hormone levels and immune response. Notably, these atypical biological profiles are linked to behavioral indexes of compromised social and mental health, including poor relationships with age mates (less social affiliation, more affective withdrawal, more subordinate behavior), heightened manifestations of emotional distress and anxiety, impulsive and aggressive behavior, and alcohol tolerance. Of interest, the adverse biological and behavioral consequences of early social experience appear to be moderated by genetic variation, such that only monkeys with certain genetic profiles show these effects (for a review, see Suomi, 2008).

Despite these groundbreaking advances, far less effort has been dedicated to documenting directly (through longitudinal studies of mediation) whether socially driven biological reorganization accounts for the mental health consequences of early social adversity. Moreover, the possibility of rGE correlations and epigenetic effects lends further complexity to theoretical models, as experiences thought to independently create changes in the brain may themselves be constructed through evocative or active genetic effects on the environment or may merely activate underlying genetic propensities toward biological dysregulation, calling for research designed to tease apart these alternative developmental processes.

Social-Cognitive Pathways

Diverse theoretical perspectives share the proposition that social-cognitive processes serve as long-term carriers of early interpersonal experience and as potential vehicles of risk for psychopathology. Common across these perspectives is the notion that individual differences in cognitive formulations of the social world find their roots in past interpersonal experiences. Prior experiences are believed to be transformed into abstract, intrapsychic representations, variously described as internal working models (Bowlby, 1980), cognitive-interpersonal schemas (Baldwin,

1992), or mental databases (Crick & Dodge, 1994). These cognitive-affective structures, which incorporate beliefs and evaluations about the self and others, are encoded in memory early in life and become increasingly intransigent over time. As they consolidate, they become a lens through which future interpersonal experiences are encoded, interpreted, and retrieved, thereby coloring individuals' perceptions and expectations about themselves and their social worlds. When formed in the context of stressful interpersonal experiences, these mental models presumably foster adverse responses to the environment and a consequent vulnerability to psychopathology. Indeed, maladaptive social-cognitive processes are implicated in theories of many forms of psychopathology, including depression, anxiety, and aggression/antisocial behavior.

According to cognitive theories of depression, risky early family environments (e.g., insensitive caregiving, interpersonal loss, maltreatment, parent psychopathology) foster mental models of the self as incompetent, unlovable, and helpless and of the world as hostile (for reviews, see Abela & Hankin, 2008; Gibb & Coles, 2005; Rudolph & Flynn, 2014). These maladaptive schemas may take one of two forms. Autonomous (Beck, 1987) or self-critical (Blatt & Homan, 1992) individuals adopt perfectionistic standards and suffer from fears of criticism, inferiority, and failure. Sociotropic (Beck, 1987) or dependent (Blatt & Homan, 1992) individuals adopt feelings of helplessness and suffer from fears of loss, rejection, and abandonment. These schemas are believed to create vulnerability to depression in the face of relevant life stressors (e.g., failure vs. rejection). Cognitive theories of anxiety assert that exposure to uncontrollable social experiences or adverse family contexts (e.g., insecure attachment, overprotective parenting) foster mental models characterized by low self-efficacy and vigilance to threat (Kerns, 2008; Nolte, Guiney, Fonagy, Mayes, & Luyten, 2011). Cognitive theories of aggression postulate that family adversity (e.g., harsh parenting, maltreatment) and peer adversity (e.g., rejection) are internalized as social information-processing biases characterized by hostile processing of social cues and deviant social goals (Dodge, Bates, & Pettit, 1990). Collectively, these theories presume that social-cognitive schemas and associated information processing biases become engrained over time and modulate how individuals react to future social experiences, serving as proximal contributors to psychopathology.

Despite the prevalence of theories suggesting that early interpersonal experiences shape social-cognitive processes, there is evidence for genetic, biological, and temperamental contributions to cognitive biases (Dodge & Pettit, 2003; Hammen et al., 2014; Nolte et al., 2011). Future theory development and validation must therefore consider the extent to which a common genetic liability underlies exposure to stressful interpersonal experiences, maladaptive social-cognitive processes, and particular forms of psychopathology as well as how genetic and environmental factors independently or interactively contribute to social-cognitive risk processes.

Emotion Pathways

Emotion processing can be construed as a range of processes involved in the recognition, understanding, regulation, and expression of emotional cues (Pollak, 2008). Difficulties processing and regulating emotions lie at the core of psychopathology. Efforts to understand the interpersonal origins of such difficulties have focused on identifying how social adversity shapes psychological, neural, and biological processes central to emotional experience, which in turn serve as proximal risks for disorder.

At a phenomenological level, relationships are thought to shape emotions through both explicit and implicit pathways. Emotional tendencies may be directly transmitted from parents to offspring through modeling (e.g., emotional contagion), instruction (e.g., scaffolding and socialization of emotion), and reinforcement (Davies & Sturge-Apple, 2014), creating an avenue for the intergenerational transmission of psychopathology (Abaied & Rudolph, 2014; Vasey et al., 2014). Interpersonal experiences also may indirectly foster certain patterns of emotion regulation and expression. Attachment theory provides one prototype of this process. The attachment relationship is presumed to provide children with a context in which they learn strategies for identifying, regulating, and expressing emotions. Avoidant attachment confers a tendency toward deactivating responses to stress, in which youth suppress negative emotions, whereas anxious attachment involves a tendency toward hyperactivating responses to stress, in which youth amplify outward signals of distress (Weinfield et al., 2008). Insecure attachment and problematic family environments (e.g., conflict exposure) also may undermine youths' emotional understanding and sense of emotional security (Davies & Sturge-Apple, 2014; Thompson, 2008). These maladaptive patterns of emotional experience and regulation can coalesce into psychopathology (Abaied & Rudolph, 2014; Davies & Sturge-Apple, 2014).

Adverse interpersonal experiences also alter sensory thresholds for the processing of emotion. Youth exposed to maltreatment show heightened sensitivity to facial cues of anger (but not other emotions), suggesting their emotion

processing systems become attuned to cues that are salient within their unique interpersonal contexts (Pollak, 2008). This perceptual salience influences attention control processes involved in emotion as reflected in rapid orienting to, and delayed disengagement from, anger cues. Perceptual sensitivity to threat cues, hypervigilance, and associated self-protective emotional processes also may emerge in other risky family contexts (Davies & Sturge-Apple, 2014). In turn, cognitive regulatory biases in emotion processing (e.g., heightened attention to anger cues and diminished attention to fear and sadness cues) may serve as proximal risks for aggression and antisocial behavior. In a similar fashion, youth exposed to maternal depression show emotion processing biases characterized by selective attention to negative versus positive facial expressions, a pattern that likely places these youth at risk for depression (Joormann, Eugene, & Gotlib, 2009).

Social adversity also can contribute to risk for psychopathology by undermining developing neural circuitry guiding emotion regulation and processing (for a review, see Gunnar, 2010). Youth exposed to stressors such as maltreatment and parent psychopathology show characteristic differences in the neuroanatomical and neurophysiological substrates of emotion that presage risk for psychopathology. Maltreated youth display smaller prefrontal cortex and right temporal lobe regions, disrupted neural processing of emotional stimuli, heightened autonomic reactivity to conflict, and atypical patterns of hormones involved in stress reactivity and affiliative bonding, all differences with potential implications for emotion processing and responding; monkeys raised in isolation show decreased white matter in parietal and prefrontal cortices, areas linked to emotional modulation (for reviews, see Cicchetti & Banny, 2014; Pollak, 2008). Offspring of depressed mothers show dysregulation of the HPA axis, which in turn predicts subsequent youth depression, and atypical activation in brain regions (e.g., amygdala, nucleus accumbens, prefrontal cortex) associated with emotion regulation (for a review, see Joormann et al., 2009).

From a developmental perspective, understanding emotional pathways linking interpersonal experience and psychopathology becomes particularly important during adolescence, a stage marked by notable changes in the neural and cognitive systems underlying emotions (Lewis, Lamm, Stieben, & Zelazo, 2006) along with increases in many forms of psychopathology. Moreover, it is important to consider that emotional sensitization may change across development, as chronic exposure to stressful interpersonal experiences can eventually result in habituation of psychological and biological response systems and consequent inhibition of reactivity (Davies & Sturge-Apple, 2014). Thus, profiles of emotional risk may shift across development with ongoing exposure to social adversity. Long-term research must track the emotional consequences of social adversity over time to determine whether effects are enduring and crystallize into identifiable forms of psychopathology.

Summary

This section summarizes several intermediary processes that can serve as mechanisms through which exposure to social adversity crystallizes into psychopathology across development. Despite supportive circumstantial evidence (i.e., social adversity predicts disruptions in biological, social-cognitive, and emotional processes; these disruptions instill risk for psychopathology), definitive tests of these models need to directly examine the proposed mediational pathways and to evaluate potential changes in the transactions among social risk, mediators, and psychopathology across development. To determine the strength of psychosocial transmission of risk, research also needs to sort out the rGE correlations and epigenetic effects that could account for linkages between the social environment and mediating processes.

DISORDER-SPECIFIC INTEGRATIVE INTERPERSONAL THEORIES OF PSYCHOPATHOLOGY

Despite the insights afforded by the aforementioned interpersonal theories, each solves only one piece of the multifaceted puzzle of psychopathology. Embracing the defining axioms of developmental psychopathology, integrative interpersonal theories consider how risk and protective factors within youth and their environments along with relevant moderators and mediators contribute through additive, multiplicative, and transactional processes to trajectories of risk or resilience across contexts and over time. Integrative developmental models also consider how risk evolves across different stages, determining the timing of onset and trajectories of psychopathology at certain points in the life course. Although the literature is rich with many integrative models of developmental psychopathology, we focus selectively on those that have a core interpersonal component. Given their abundance in the literature, we present integrative models of three groups of disorders: depression, anxiety, and externalizing psychopathology.

Integrative Interpersonal Theories of Depression

In many ways, it is difficult to disentangle youth depression from the interpersonal context in which it evolves. Although the depressive syndrome incorporates many subjective and internal experiences—such as sadness, boredom, low self-worth, concentration difficulties, and fatigue—these symptoms often are expressed within, and intricately linked to, interpersonal interactions and relationships. Indeed, depressed youth experience a wide assortment of personal deficits and social disturbances that illustrate the interpersonal nature of the disorder (for reviews, see Rudolph, 2009; Rudolph et al., 2008). Their self-views are marked by feelings of social inadequacy and perceived rejection; significant others also view them as lacking in key social skills and as undesirable relationship partners. Moreover, depressed youth often encounter either overt conflict and rejection or social isolation. Given these many forms of social disruption, it is not surprising that contemporary theory and research on youth depression incorporate a strong interpersonal focus. Because interpersonal models have their grounding in early clinical and research perspectives on adult depression, we briefly describe these pioneering theories and then explore developmentally sensitive adaptations and extensions.

In one of the first cohesive interpersonal theories of depression, Coyne and colleagues described a "depressive social process" (Coyne, 1976, p. 187) wherein depression-linked characteristics and behaviors disrupt social relationships by eliciting negative responses from social network members, which contribute to the onset, maintenance, and recurrence of depression (Joiner & Timmons, 2009). The process begins when depressed individuals seek encouragement and reassurance of their worth. Because of their low self-worth and skepticism, depressed individuals question the encouragement and reassurance provided by others and thus they continue to seek reassurance. Failure to accept offered support eventually causes frustration and rejection by relationship partners. As depressed individuals observe inconsistencies between others' reassurances of support and their rejecting behavior, depressive symptoms increase. An ongoing cycle emerges, fueled by continued rejection and validation of negative self-views accompanied by ensuing intensification of depressive symptoms.

Paradoxically, depressed individuals also engage in negative feedback seeking, a process wherein they explicitly seek out negative feedback and criticism. According to self-verification theory (Swann, 1990), individuals are motivated by a need to maintain consistent self-views, causing them to seek information that confirms these views. In the case of depressed individuals, they elicit feedback consistent with their negative self-schemas, perhaps by affiliating with people who evaluate them negatively, despite the potential pain they experience when this feedback is provided (Swann, Wenzlaff, Krull, & Pelham, 1992). Of course, this negative feedback undoubtedly reinforces their low self-worth. Thus, the continuity of depression can be explained by a "self-propagatory process" (Joiner & Timmons, 2009, p. 332), wherein behavioral manifestations and consequences of depressive symptoms elicit maintaining responses from the environment (rejection, withdrawal of social support, negative feedback), which lengthen episodes and trigger recurrence of symptoms.

This pioneering theory, along with its extensions (Joiner & Timmons, 2009) and intellectual relatives (e.g., Hammen, 2006), provide a useful grounding for understanding the interpersonal context of youth depression but are constrained by their adevelopmental focus. Specifically, they fail to (1) articulate the origins of interpersonal vulnerability; (2) consider which interpersonal processes are relevant during particular life stages; and (3) elucidate how normative developmental changes interact with individual differences in interpersonal traits and experiences to account for the emergence of depression. To address these conceptual lacunae, recent developmentally sensitive interpersonal theories offer several innovations. First, these theories provide dynamic frameworks that consider how complex interactions and transactions among youth and their social contexts contribute to the emergence and expression of interpersonal vulnerability over time. Second, they consider how the interpersonal antecedents and consequences of depression crystallize during developmentally salient stages, particularly the transition through adolescence, with a focus on how normative challenges set the stage for interpersonal vulnerability to depression. In this vein, these theories address two well-established developmental features of depression: the surge in depression and the emergence of a sex difference in depression during adolescence. Third, interpersonal theories of youth depression clearly account for continuity in depression over time, explaining how characteristics of depressed youth shape their social contexts in ways that perpetuate and exacerbate symptoms in the short- and long-term.

Nolen-Hoeksema and Girgus (1994) provided one of the first broad frameworks for understanding the emerging sex difference in depression across adolescence. According to this framework, girls carry greater vulnerability than boys prior to adolescence; this vulnerability interacts with girls' heightened exposure to challenges relative to boys during adolescence to predict a sharper surge in

depression. Although this framework focuses on a broad range of vulnerabilities and adolescent challenges, personal and contextual influences of an interpersonal nature (e.g., interpersonal orientation, exposure to social challenges such as sexual abuse) assume a central position (see also Nolen-Hoeksema, 2001).

Two other theories focus on more precise interpersonal processes through which sex-linked vulnerability to depression unfolds across the adolescent transition. Cyranowski, Frank, Young, and Shear (2000) highlighted how girls' affiliative needs, driven by both social and hormonal forces, interact with social challenges during the transition to foster depression in at-risk females. Similarly, Rudolph (2002) suggested that girls' heightened exposure to, generation of, and reactivity to interpersonal stress contribute to the emergence and maintenance of a sex difference in depression during adolescence. Female-linked relational orientation styles (e.g., a heightened psychological and emotional investment in relationships) are presumed to account in part for the sex difference in stress reactivity and depression. These two models shed light on interpersonal vulnerability in adolescent girls but are somewhat limited in scope.

Considering a wider spectrum of interpersonal vulnerabilities and challenges, Rudolph and colleagues (Rudolph, 2009; Rudolph et al., 2008) recently offered a broader developmentally based, interpersonal model explaining the emergence of depression and the sex difference therein during adolescence (Figure 7.2). This model proposes that early family adversity (e.g., insecure parent–child attachment, parental depression, maltreatment) fosters the development of maladaptive appraisals of relationships and social-behavioral deficits. These appraisals and deficits heighten vulnerability to depression, particularly in the face of relationship disturbances, and cause youth to generate stress in their existing relationships and to select into more stressful social contexts. The contributions of maladaptive relationship appraisals and social-behavioral deficits to depression are intensified during the passage through adolescence, especially in girls, due to accompanying maturational changes. Finally, depression exacerbates interpersonal dysfunction, accounting for the continuity of depression over time.

Within this model, maladaptive relationship appraisals are conceptualized as negative conceptions of relationships (negative perceptions of self and others,

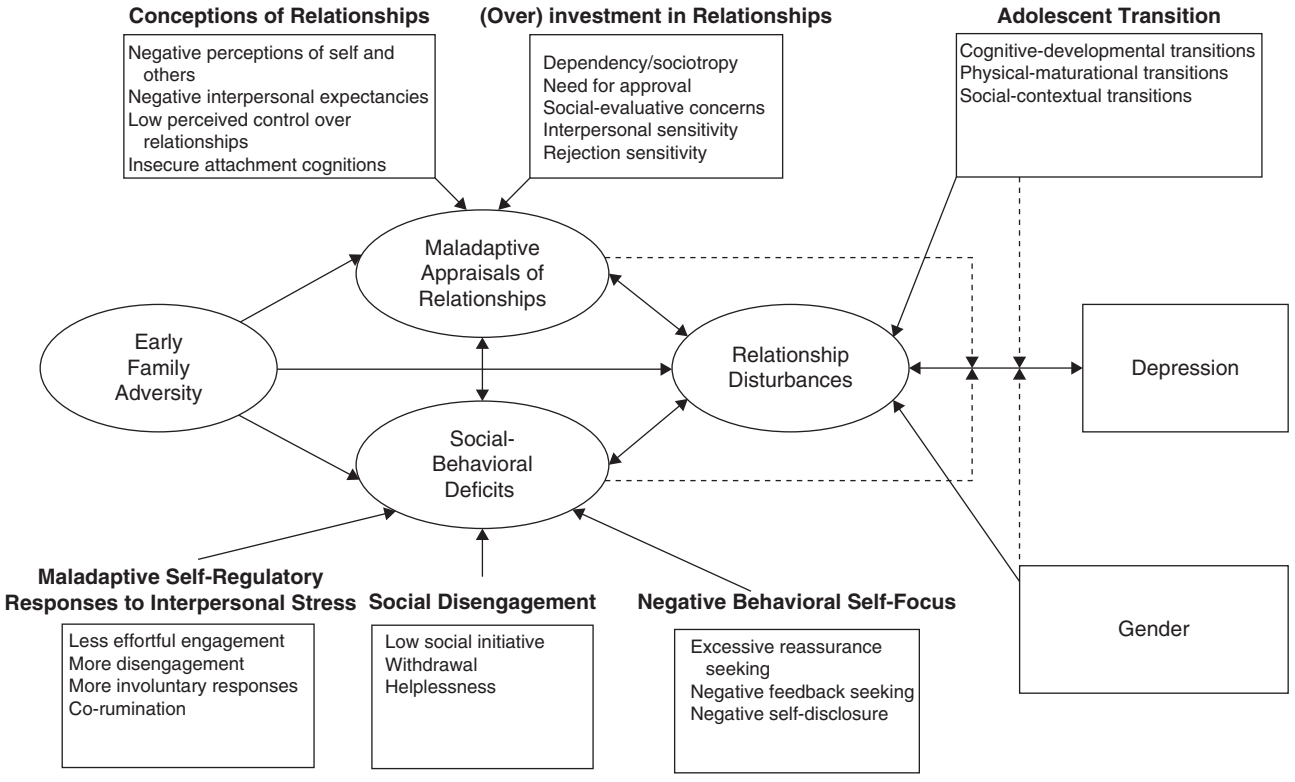


Figure 7.2 Theoretical model of the interpersonal context of adolescent depression. *Source:* Reprinted from K. D. Rudolph, The interpersonal context of adolescent depression, in S. Nolen-Hoeksema & L. M. Hilt (Eds.), *Handbook of depression in adolescents (*pp. 377–418), New York, NY: Routledge, 2009.

pessimistic interpersonal expectancies, low perceived control over relationships, and insecure attachment cognitions) and an overinvestment in relationships (dependency/sociotropy, need for approval, social-evaluative concerns, and interpersonal/rejection sensitivity). Social-behavioral deficits are conceptualized as maladaptive self-regulatory responses to interpersonal stress (less effortful engagement and more effortful disengagement; involuntary, dysregulated responses; and co-rumination), social disengagement (low social initiative, withdrawal, and helplessness), and a negative behavioral self-focus (excessive reassurance seeking, negative feedback seeking, and negative self-disclosure). Relationship disturbances include low social status (e.g., less peer acceptance and more peer rejection), negative responses from interaction partners, poor friendship quality, disturbances in romantic and family relationships, and general interpersonal stress.

Despite having some roots in interpersonal theories of adult depression, this model departs from these theories in several ways. First, it incorporates the direct and indirect effects of maladaptive relationship appraisals, proposing that they help to account for the generation of stress and conflict in relationships and they moderate the effect of relationship disturbances on depression. Second, this model focuses on developmentally salient interpersonal processes, emphasizing those particularly relevant to girls' increasing risk relative to boys across adolescence (e.g., social-evaluative concerns and interpersonal sensitivity). Third, this model articulates how the social-contextual, physical-maturational, and cognitive-developmental transitions of adolescence intensify interpersonal vulnerability and depression, particularly in girls, during this stage. Specifically, it is proposed that the following changes trigger depressive symptoms in youth with prior interpersonal vulnerability: (1) broader and more proximal changes in social contexts (e.g., school transitions, increasing individuation from the family and immersion in the peer group, entrance into romantic relationships); (2) physical, psychological and social effects of puberty (e.g., hormonal changes, alterations in self- and other-perceptions, changing social roles and stressors); and (3) advancing cognitive abilities (e.g., heightened social comparison, generalization across situations and time, and perspective taking). Each of these transitions is presumed to pose particular challenges to girls, who experience more social challenges, more adverse effects of puberty, and heightened investment in the quality of relationships and judgments of others. Finally, this model considers how, in developing youth, symptoms can create proximal disturbances in relationships as well as long-term interpersonal scars that threaten future development and adaptation (Rudolph, 2009).

Hammen and colleagues (2004) proposed a model describing interpersonal processes that account for the intergenerational transmission of depression. This model focuses on the stressful family environment associated with maternal depression and its consequences for youths' interpersonal functioning. In particular, maternal depression manifests in interpersonal stress and poor parenting in mothers; through modeling and socialization processes, offspring develop social deficits that precipitate their generation of stress within relationships; these deficits and stressors serve as proximal predictors of youth depression.

Taking a broader perspective, Cicchetti and Toth (1998) presented an integrative ecological transactional model of depression that incorporates the interface among multiple biological, psychological, and social systems. This model espouses an organizational approach to development, considering how challenges to the achievement of four stage-salient tasks (biological regulation, affective differentiation and modulation of arousal and attention, secure attachment and positive representational models, and a healthy self-system) along with predisposing genetic characteristics increase the likely emergence of a depressotypic organization. Interpersonal themes permeate this model, as reflected in the prominent role of parent–child interactions in guiding adaptation within each of these domains and the potential enduring pernicious effects of biological, affective, and psychological disruptions on the development of adaptive interpersonal relationships. Moreover, the emergence of depression is considered within the context of the microsystem (family transmission of psychopathology and other stressors in family relationships), exosystem (school and community contexts), and macrosystem (e.g., cultural values and beliefs).

Integrative Interpersonal Theories of Anxiety

Traditional etiological theories of anxiety focused on intrapersonal (e.g., cognitive, affective, behavioral, physiological, and genetic) processes; yet, like depression, many symptoms of anxiety manifest within an interpersonal context and undoubtedly influence youths' interpersonal relationships. In some anxiety disorders (e.g., social phobia), interpersonal dysfunction is a fundamental feature; in others, interpersonal worries may be a central characteristic (e.g., generalized anxiety disorder) or symptoms may prevent the development of healthy relationships or cause tension within existing relationships (e.g., separation

anxiety disorder, agoraphobia). Indeed, anxious youth experience many social disturbances, including problems in parent–child relationships, social withdrawal and avoidance, fear of rejection, lower levels of peer acceptance, and peer exclusion and victimization (for reviews, see Davila et al., 2010; La Greca & Landoll, 2011). The interpersonal context of anxiety may become particularly salient during formative stages, such as the adolescent transition, when relationships become more diversified, complex, and challenging.

One recent model (Murray et al., 2009) considers the interactive influences of (1) genetic and biological vulnerability (expressed in the form of temperamental behavioral inhibition as well as information processing biases, such as attentional bias to threat and biased interpretation of ambiguous information); (2) exposure to adverse life events that heighten perceptions of threat and dampen perceptions of control; (3) parental anxiogenic modeling, instruction, and transfer of information about threat; and (4) parenting characterized by overinvolvement and discouragement of autonomy. These risk factors are thought to stem, in part, from parental anxiety, accounting for the intergenerational transmission of disorder. However, the model also assumes transactional processes wherein parental behaviors are elicited by pre-existing vulnerabilities in youth, a process that is particularly likely in families with anxious parents.

Another contemporary model (Nolte et al., 2011) provides a compelling multidisciplinary developmental framework integrating attachment and parenting theories of anxiety with perspectives drawn from the fields of social neuroscience, genetics, and neurobiology (Figure 7.3). At the core of this framework lie stress-regulatory strategies that enhance reactivity to threat-related cues and experiences. These individual styles of threat response and stress regulation are believed to develop and continuously operate within the context of caregiving experiences as instantiated in attachment relationships. Thus, attachment experiences are viewed as an organizational system that modulates the expression of genetic/temperamental, epigenetic, and environmental risks for anxiety.

In particular, attachment relationships characterized by inconsistency and unpredictability in caregivers and anxious-ambivalent attachment in offspring drive hyperactivation in the child, as reflected in an overly sensitive HPA axis and allostatic overload, altered fronto-limbic neural circuitry, attentional bias to threat, low personal agency, poor mentalization (ability to perceive the mental states of others), and hypervigilance; this hyperactivating profile compromises youths' ability to accommodate to future stressors, setting the stage for anxiety. This model also addresses the intergenerational transmission of anxiety, proposing that parents' own anxiety-prone risk profile—characterized by low social support, insecure

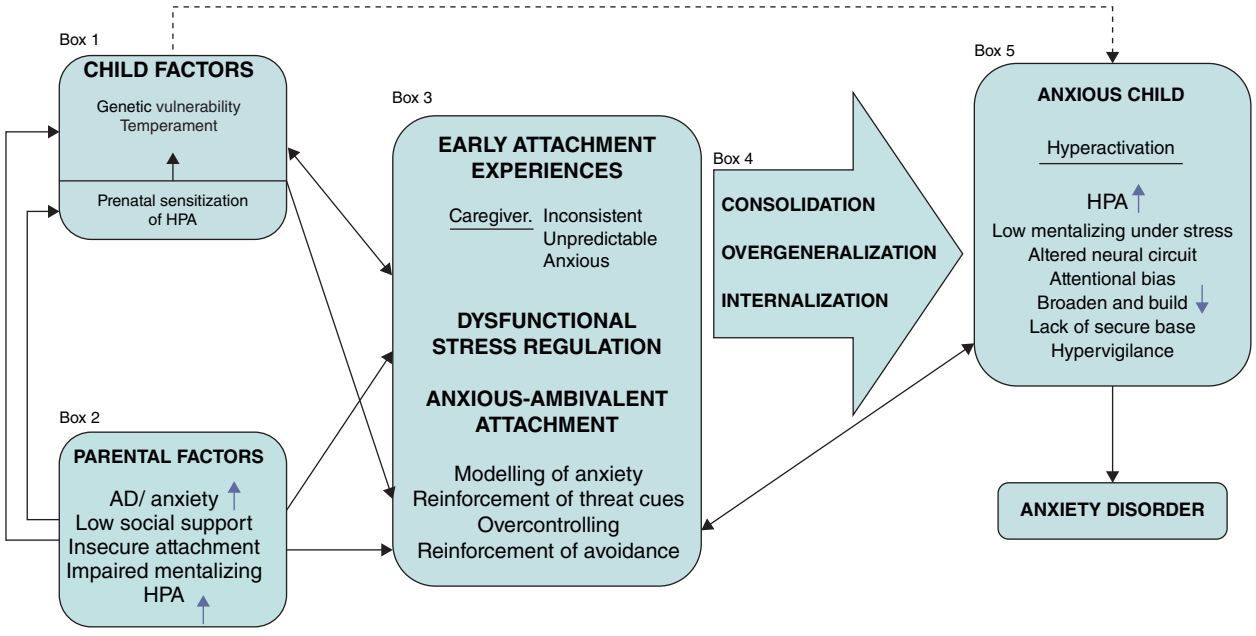


Figure 7.3 A developmental model of the attachment-moderated interaction of risk factors in the development of anxiety disorders. See footnote 1. *Source:* Reprinted from T. Nolte, J. Guiney, P. Fonagy, L. C. Mayes, & P. Luyten, Interpersonal stress regulation and the development of anxiety disorders: An attachment-based developmental framework, *Frontiers in Behavioral Neuroscience, 5*, 1–21, 2011.

attachment, impaired mentalization, and heightened HPA reactivity—interferes with adaptive parent–child co-regulation of distress and drives the development of poor self-regulation in offspring. Moreover, maternal anxiety may influence the developmental programming (i.e., sensitization) of the HPA axis through its effects on maternal stress and ensuing levels of prenatal cortisol. This constitutionally based reactivity in offspring interacts with later attachment experiences and parenting styles (e.g., modeling and reinforcement of avoidance, overcontrol) to determine risk for impaired stress regulation processes.

Arising from a distinct intellectual tradition, developmental scientists offer theoretical explanations for how anxiety develops within the context of temperamental risk, maladaptive parenting practices, and ensuing compromised relationships with peers. Such models emerge from efforts to understanding the precursors and consequences of social withdrawal, particularly as motivated by shyness, inhibition, harm-avoidance, and fear. Rubin and colleagues (2009) presented one such model, wherein a cascade of transactions among youth vulnerabilities, parental responses, and peer difficulties eventuate in social anxiety and social phobia by adolescence. The cascade begins with infant temperamental risk in the form of a lowered threshold for arousal and difficulty to soothe. This temperamental style elicits vigilance and overly solicitous behavior by parents, which maintains or intensifies the child's constitutional tendency toward wariness and inhibition during the toddler and preschool years. As children enter more complex and evaluative social relationships during elementary school, the behavioral expression of this inhibition (e.g., social reticence, avoidance of peer interactions) elicits peer rejection and victimization, which reinforce social concerns, amplify withdrawal, and trigger negative self-regard (e.g., self-blame, hopelessness). Socially withdrawn youth then enter into poor quality friendships with similar peers, further inhibiting their development of adaptive social skills. Parents respond through overprotective and power-assertive behavior (e.g., discouraging independence, controlling social activities), which reinforces children's sense of insecurity and low social efficacy and interferes with their learning of coping and problem-solving skills. Ultimately, social inhibition and negative self-regard transform into social anxiety and social phobia during adolescence. Of note, this model allows for a deflection from this escalating trajectory of risk in the presence of responsive and warm parent–child relationships or school contexts (e.g., positive teacher-child relationships or classroom environment).

Integrative Interpersonal Theories of Externalizing Psychopathology

Patterson and colleagues' (1991) early versus late starter model of the development of aggressive and antisocial behavior has been one of the most influential integrative models guiding the understanding of the development of externalizing psychopathology. This model distinguishes youth whose antisocial behavior begins during childhood (early starters) versus adolescence (late starters). According to the theory, early starters are at greater risk for long-term antisocial behavior that extends into adulthood than are late starters.

This theory stresses the importance of coercive exchanges between parents and children over time in the development of aggressive behavior. These early coercive exchanges serve as a basis for early-starting antisocial behavior. Children may generalize to interactions with peers' coercive interaction styles initially learned through parent–child interactions. Many children who have experienced coercive episodes in the family have social skill deficits that contribute to rejection by peers during elementary school. Peer rejection then further contributes to early starting antisocial behavior. Patterson et al.'s (1991) model thus describes how coercive parent–child interactions and peer rejection set the stage for aggressive children (early starters) to remain chronically antisocial into adulthood.

Late starters who become antisocial during adolescence are theorized to experience poor parental monitoring and supervision, aspects of parenting that become more salient during adolescence. Poor monitoring and lack of supervision contribute to increasing involvement with deviant peers, which in turn promotes adolescents' own antisocial behavior. In contrast to early starters, late starters have developed sufficient social and academic skills so they can desist from antisocial behavior when changes in the environment make other options more appealing.

Moffitt's (1993) life-course persistent versus adolescent limited model shares several key features with Patterson et al.'s (1991) model. Both theories differentiate between the etiology of externalizing problems that begin in childhood versus adolescence, and both include family and peer risk factors for externalizing psychopathology. However, whereas Patterson's theory emphasizes coercive parenting during childhood, Moffitt's theory emphasizes early emerging neuropsychological deficits such as poor verbal skills, inattention, and impulsivity. These characteristics make children more difficult to parent; in environments of risk and adversity, parents may lack the psychological and physical resources to manage a difficult child.

In Moffitt's theory, this dual risk of a difficult child situated in an adverse environment lays the foundation for life-course-persistent antisocial behavior. When these children enter school, they often struggle academically and socially, furthering their risk for the development of externalizing problems.

In contrast to Patterson et al.'s (1991) focus on poor parental monitoring and supervision along with deviant peer affiliation as the driving forces behind late starting antisocial behavior, Moffitt (1993) regarded adolescent-limited antisocial behavior as resulting from a maturity gap between adolescents' dependence on and control by adults and their desire to demonstrate their freedom from adult constraint. However, as they continue to develop, and legitimate adult roles and privileges become available to them, there are fewer incentives to engage in antisocial behavior. Because these adolescent-limited offenders do not have the neuropsychological deficits or problematic family environments characteristic of life-course-persistent offenders, they are able to take advantage of new opportunities with the transition to adulthood. Thus, adolescent-limited antisocial behavior is regarded as resulting from normative forces to which all adolescents are exposed if they are in a maturity gap. Of note, some more recent evidence does suggest that late-starting and adolescent-limited forms of antisocial behavior may not be as innocuous as once believed, and in some cases adolescents with these profiles proceed along long-term trajectories of risk (Marmorstein & Iacono, 2005).

Both Patterson et al.'s (1991) and Moffitt's (1993) theories could be considered forms of a broader category of developmental cascade models that describe how a constellation of interpersonal and other risks unfold over time to confer risk for the development of externalizing psychopathology. For example, Dishion (2014) presented a cascade model in which defiance and self-regulation difficulties in early childhood develop into overt and covert antisocial behavior during middle childhood and into substance use, risky sexual behavior, and serious problem behaviors during adolescence. As part of this cascade, academic problems, peer rejection, and affiliation with at-risk peers during childhood along with school failure and deviant peer contagion during adolescence perpetuate and augment these cascades of externalizing problems. Poor family management, insufficient parental monitoring, and other ecological risks also contribute to the cascade. Likewise, Dodge et al. (2009) delineated a developmental cascade model for the onset of illicit substance use in which difficult child characteristics and an adverse sociocultural context contribute to early parenting problems, which lead to early child behavior problems and consequent peer adversity, which contribute to parenting problems during adolescence, which lead to adolescent peer problems and eventually to illicit substance use. In these integrative cascade models, intergenerational continuity in externalizing problems can result from genetic risk conferred by parents who themselves have externalizing problems as well as from environmental risk created by parents with externalizing problems, who are more likely to use harsh, inconsistent discipline and less likely to be warm, responsive, and sensitive.

These recent cascade models are foreshadowed by other multifactorial developmental models. For example, Greenberg and colleagues (1993) presented one early integrative interpersonal model for conceptualizing the early onset of disruptive behavior problems (see also DeKleyen & Greenberg, 2008). Focusing on multiple pathways and levels, this model includes four domains of risk: insecure attachment, ineffective parenting (e.g., harsh and ineffective discipline, lack of warmth), high family adversity (e.g., low SES, marital conflict, trauma, poor social support), and atypical child characteristics (e.g., poor executive function, temperamental reactivity). An emphasis is placed on the creation of person-centered profiles that consider how these risks combine additively or multiplicatively to determine behavioral trajectories, with the assumption that no one risk factor is necessary or sufficient for the development of psychopathology. The model also allows for early and emerging associations among risk factors, significant changes in risk status across development, and ongoing transactions between risks and disruptive behavior over time. These complex processes presumably result in multiple pathways to disorder that depend on the number, type, and combination of risk factors present and their developmental timing.

Dodge and colleagues (e.g., Crick & Dodge, 1994; Dodge et al., 1990) enriched integrative models of externalizing psychopathology by specifying the role of social-cognitive processes. Like many other integrative theories, Dodge and Pettit's (2003) biopsychosocial model (Figure 7.4) of the development of chronic conduct problems includes children's biological predispositions, the sociocultural context, parenting, and peers as risk factors for the development of conduct problems. However, their model further posits that mental processes, including social knowledge structures and social-information-processing patterns, mediate the links between these early risks and subsequent conduct problems. That is, biological predispositions, sociocultural contexts, and previous social experiences shape children's knowledge about the world in ways that have implications for their future behavior. On the basis of these knowledge structures, children

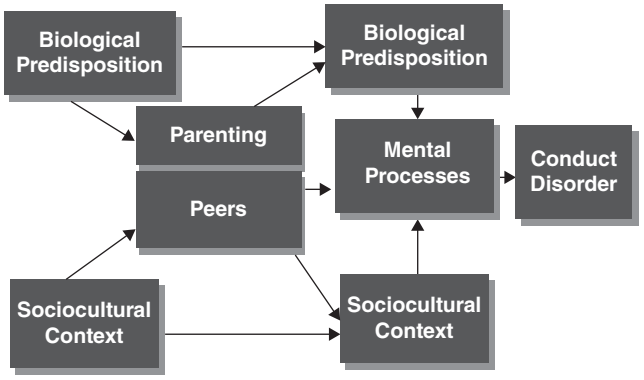


Figure 7.4 A biopsychosocial model of the development of conduct disorder. *Source:* Reprinted from K. A. Dodge & G. S. Pettit, A biopsychosocial model of the development of chronic conduct problems in adolescence, *Developmental Psychology, 39*, 349–371, 2003.

engage in a series of cognitive steps when they encounter new social stimuli, including encoding social information, making attributions about the causes of others' behavior, generating possible responses, and evaluating responses. Biases at any of these processing steps increase the risk of antisocial behavior.

Although sex differences in externalizing psychopathology are well documented (Archer, 2004), it is unclear whether etiological pathways differ for boys and girls. Patterson's theory was developed on the basis of an exclusively male sample. The sample that formed the basis of Moffit's (1993) theory included both males and females, yet the theory itself was intended as an explanatory framework for understanding the development of antisocial behavior among boys. Silverthorn and Frick (1999) reviewed the literature on the development of antisocial behavior in girls and concluded that modifications to the distinction between early and later onset of antisocial behavior may be needed. In particular, the authors concluded that girls' antisocial behavior may not emerge until adolescence, despite the presence of risk factors such as neuropsychological deficits and dysfunctional family environment that would predict childhood onset for boys. Silverthorn and Frick liken this delayed onset pathway for girls to the childhood-onset pathway for boys. Furthermore, they posit that an adolescent-onset path with relatively benign consequences (as proposed by Moffit) does not exist for girls. These interesting theoretical propositions await rigorous empirical testing.

FUTURE DIRECTIONS

Reflecting historical perspectives on the integral role of interpersonal relationships in human adaptation, the field of developmental science has long emphasized early experience within relationships as a context and a catalyst for psychological growth. It is increasingly clear that interpersonal relationships throughout childhood, adolescence, and beyond also can play an important role in individual adjustment. In a recent summary of research on resilience and positive psychology, Luthar, Lyman, and Crossman (2014) concluded that the most salient theme to emerge from these fields is the fundamental value of human relationships. If a need to belong is at the heart of psychological health and well-being, interpersonal alienation and disruption likely lie at the core of psychopathology. Indeed, this notion has permeated the field since the early writings of Freud (1916), Bowlby (1969), and many others, and continues to characterize many contemporary theories of developmental psychopathology. As such, it is now widely accepted that a variety of interpersonal perturbations can create significant obstacles to healthy development. How, then, can and should the field progress as we continue to unravel the mystery of why, how, and when psychopathology emerges, develops, and persists within interpersonal contexts? Within each of the earlier sections, we pointed out several specific areas for advancement; here we focus on more general directions that we believe should serve as a cornerstone for interpersonal theories of psychopathology in the next decade.

Developing and Testing Multilevel Conceptualizations

One of the most universally recognized and commonly cited contemporary themes in the field of developmental psychopathology is the need for multilevel conceptualizations, reflecting mounting pressure for interdisciplinary perspectives that consider the interface among biological, psychological, behavioral, and interpersonal systems of development (Cicchetti, 2008). At the risk of sounding mundane, we propose that this venture should indeed be one of the driving forces for upcoming development of interpersonal theories and for designing effective empirical investigations to test these theories.

As we briefly mention in the chapter, the field has made promising inroads into documenting gene–environment correlations and interactions as well as beginning to understand epigenetic processes within interpersonal contexts. What this means is that there is good reason to believe that genes influence both exposure and reactivity to social experiences and that social experiences influence gene expression, thus dramatically enriching our understanding of the interpersonal context of psychopathology. In the coming years we will likely see interpersonal theories evolve to further postulate the biological and psychological endophenotypes through which early social adversity and contemporaneous interpersonal experiences leave their

legacy on gene expression. This elaboration will require specific, testable mechanisms amenable to direct validation, thereby bolstering our increasingly conceptually rich theories with equally compelling empirical evidence.

Elucidating Developmental Pathways

Building upon multilevel interpersonal theories also will require more precise explication of developmental timing effects and the possibility of developmental plasticity in the face of interpersonal adversity. Several questions will need to be addressed in this regard. What is the relative contribution of early versus chronic versus acute interpersonal adversity on psychopathology? Do early adverse interpersonal experiences have enduring effects beyond those linked to ongoing stressors? Are there stages of development (e.g., puberty, transition to adulthood) during which the pernicious effects of early adversity are intensified or open to reversal? What factors promote resilience against these effects? What are the mediating processes that account for long-term effects of gene–early environment interactions and how do these processes unfold over the course of development? Answering these questions will refine interpersonal models of psychopathology in ways that make them truly developmental in nature.

Emphasizing the Parent–Peer Interface

Theories of the peer context historically have been juxtaposed against theories of the parent/family context, and a parent versus peer model seems to come naturally to mind in the same kind of antithesis seen in classic nature versus nurture arguments. Early on, Sullivan's (1948/1953) psychiatric interest in peer influence was framed as an alternative to classical Freudian models where the child's personality is shaped in the home. Later, Harris's (1995) group socialization theory played up the importance of peer influence for personal adjustment at the expense of family-related phenomena. To this day, there is an element of catch-up to theories of the peer context, which historically have been less well developed than the 60-year-old tradition of research on parent–child attachment.

As demonstrated in this review, however, theories of peer influence can be organized around ecological and motivational perspectives that are broadly sympathetic to cardinal principles of developmental psychopathology, such as the importance of transactions between children and their environments as well as multiple, nested levels of influence. Behaviors like peer-directed aggression are more likely than in previous years to be seen as having both adaptive and maladaptive components, straddling boundaries between normative and atypical development. From a developmental psychopathology perspective, parent/family and peer influences on individual adjustment share the common element of constituting interpersonal systems, albeit embedded in different ecological systems with unique developmental trajectories. As with nature and nurture, parent and peer influences are likely to interact and synergistically shape individual pathways.

Another useful feature of a developmental psychopathology framework is the ease with which it can conceptualize parent and peer influences as ecologies in transaction with one another (e.g., Dishion, 2014; Parke & Ladd, 1992). In line with ecological postulations of mesosystemic and exosystemic factors involving multiple contexts, the synchronies (or lack thereof) between developing peer and family social ecologies, as for instance in coercive cycles generalized from home to school (Dishion & Tipsord, 2011), remain an important point of departure for future research. Further elaboration of cascade perspectives may help elucidate emerging risk across development and also link psychopathological processes arising within the family and peer contexts.

Moving from Theory to Practice

Moving from theory to practice not only in addressing psychopathology, but also in supporting youths' development in positive ways, will benefit from taking an integrative theoretical approach encompassing a number of interpersonal domains. An important future direction will be to evaluate the effectiveness of theory-based interventions designed to prevent or alleviate psychopathology. As Lewin (1952) wrote, "There is nothing more practical than a good theory" (p. 169). In this context, rather than focusing only on reversing the effects of earlier social adversity, interpersonal relationships can viewed as sources of social capital that can be harnessed to bolster children's development.

Many interventions attempt to change youth outcomes indirectly by improving parenting. Some of these interventions are driven by clear theoretical rationales; others are not. Using theory to guide interventions and then rigorously examining their effectiveness has the potential to maximize the benefits of parenting interventions in addressing risk factors for psychopathology. The success of a number of interventions such as the nurse–family partnership (Olds et al., 1998), functional family therapy (Alexander, Pugh, & Parsons, 1998), and Triple P (positive parenting program; Prinz, Sanders, Shapiro, Whitaker, & Lutzker, 2009), as well as others described as model or

promising programs in the Blueprints for Violence Prevention (Center for the Study and Prevention of Violence, 2012), suggests the promise of integrating theory, empirical research, and intervention.

With respect to peer relationships, as Ladd (2005, p. 1) stated, peers are an essential resource for children's development. Indeed, a central goal of child socialization is social integration (Maccoby, 1992), finding a supportive niche in one's contacts in the social world, and eventually, as Sullivan (1948/1953), Erikson (1950), or Bronfenbrenner (1979) might have it, being in a position to care for, sustain, and restructure that world for the better. At the same time, these theorists and others (e.g., Coleman, 1961; Mintz, 2004) often have viewed the peer social ecology with a wary eye—as bad company, far from the constraints of competent adult monitoring, and liable to lead the young person astray. A consequence of this tension is that whereas peers often are looked to as potential resources in intervention attempts—creating buddies, encouraging friendships, empowering bystanders, promoting social skills—peer-based interventions have had, since the days of the 1930s Cambridge-Somerville Project (McCord, 2003), limited success and the potential for backfiring (Dishion & Tipsord, 2011). If peers are essential ingredients to trajectories of social adjustment, can they be harnessed for positive purposes, and how can the power of peers be used to enhance individual development?

More recently in the peer domain, prevention programs such as All Starts, or Project Alert, have begun to use network perspectives that enhance social integration and the prevention of problem behaviors (Gest et al., 2011). With the advent of stochastic actor-based modeling (Veenstra et al., 2013), hopes are that researchers will be able to transcend simple declarations of homophily and be in a position to specify developmental cascades in which peer factors reflect, contribute to, and readjust life trajectories of youth (Brechwald & Prinstein, 2011; Cairns & Cairns, 1994). Within schools as well as other peer contexts (e.g., neighborhood clubs, peer group interventions), a critical question concerns the extent to which adults—such as parents—can and should scaffold and monitor peer relationships and, if so, how to do so effectively without encouraging negative effects. Even in elementary school, high status aggressive children can be an alternative authority structure to educators, parents, and other adults, challenging traditional socialization goals. Moreover, it may not be sufficient to intervene only in microsystems at the level of the peer social ecology; rather, multilevel interventions aimed at altering macrosystems (e.g., schools, communities) in which these relationships are embedded may be needed to ensure lasting effects. Research aimed at examining such assumptions in the context of specific prevention and intervention programs is sorely needed to determine the optimal way to increase the quality of social environments for a wider variety of youth, bringing out latent social capital and opportunities for growth.

Conclusion

If healthy, supportive, and emotionally satisfying relationships form a sturdy foundation on which to build the architecture of future mental health, interpersonal disruption and estrangement weaken these structures, allowing collapses in psychological well-being. Theory aimed at understanding the reasons for these breakdowns in concert with interventions aimed at bolstering interpersonal foundations hold great promise for building strong youth, communities, and societies.

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CHAPTER 8

Cognitive Risks in Developmental Psychopathology

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INTRODUCTION

> Why should we think upon things that are lovely? Because thinking determines life.
>
> —William James

Psychology is standardly defined as the study of thoughts, behaviors, and emotions. Developmental psychopathology includes the investigation of both normal and abnormal phenomena and processes in psychology. This chapter centers on thoughts, that is, cognition, in developmental psychopathology. Cognition means different things to different scholars. We focus on, and organize our review around, central mental *processes*, including attention, memory, and executive functioning, alongside core cognitive (sometimes considered social-cognitive) *products*, including attributions, attitudes, rumination, and reappraisal (see Ingram, Miranda, & Segal, 1998, for discussion of differentiating cognitive products and processes as risks to psychopathology). First, we start with a brief modern historical overview concerning the progression of how cognitive factors and processes have been conceptualized and examined from both a normal and abnormal perspective. Next, we introduce some logical conceptual models to organize our ensuing review of evidence. Then, we review the dominant cognitive risks, structured by processes and products, for several prevalent and impairing psychopathologies (internalizing disorders of depression and bipolar disorder (BD) as well as anxiety disorders, externalizing disorders of attention-deficit/hyperactivity disorder (ADHD) and conduct disorders, and schizophrenia). Space limitations did not permit a review of every cognitive risk; rather, we summarize knowledge on those main theoretically specified and empirically investigated products and processes. Finally, we discuss several points that emerged from this review and present some future research directions: (1) developmental issues; (2) the integration of cognitive products and processes within cognitive/affective neuroscience and genetics frameworks; (3) transdiagnostic versus disorder-specific models of psychopathology; and (4) translational implications.

History

The history of cognitive approaches in psychopathology has followed a curious path, best illustrated as mostly parallel play, between two predominantly independent scientific traditions: clinical psychology/psychiatry and experimental psychology/cognitive science. This theme of parallel play between clinical and cognitive science is

largely reflected up to the present, and is also mirrored in the organization of our review of cognitive influences in developmental psychopathology. More specifically, cognitive clinical scientists have tended to emphasize and study more easily accessible, self-reportable cognitive products (e.g., attributions, automatic thoughts, and dysfunctional attitudes), whereas experimental cognitive scientists have predominantly focused on cognitive processes (e.g., memory and attention) that are typically assessed via experimental tasks. Moreover, cognitive clinical scientists have tended to be more interested in and study individual differences in cognitive risks and associations with psychopathology, whereas experimental cognitive scientists have leaned more toward group differences in cognitive processes.

Both clinical and cognitive scientists followed the paradigmatic shift observed in the broad history of psychology, with the transition from psychodynamic to behaviorism and then the cognitive revolution. Broadly speaking, cognitive approaches to psychopathology have progressed through five stages: (1) descriptions and observations of how cognition is perturbed in psychopathology (Beck, 1967); (2) experiments focused on cognitive processes in aggression (e.g., Bandura, Ross, & Ross, 1961; Bandura, 1977); (3) emphasis on cognitive products (e.g., Abramson, Seligman, & Teasdale, 1978; Dodge, 1980); (4) investigations using cognitive science tasks and methods (Ingram et al., 1998) and a focus on information processing grounded in social psychology (e.g., Bandura, 1986) and emotion (e.g., Gross & Thompson, 2007); and (5) emphasis on integrating genetics (Feder, Nestler, & Charney, 2009; Gibb, Beevers, & McGeary, 2013; Swanson et al., 2007) as well as cognitive and affective neuroscience models and approaches (Beck, 2008; e.g., Bishop, 2007; De Raedt & Koster, 2010; Nigg & Casey, 2005; Posner, Russell, & Peterson, 2005).

Perhaps the most recognized clinical scientist to advance cognitive approaches to psychopathology, Aaron Beck, initiated clinical cognitive studies of psychopathology via description and observation. As a psychodynamically trained psychiatrist, he was searching for classic psychoanalytic themes of anger turned inward among the dreams of his depressed patients, but instead accurately recognized that these patients described themes of loss, failure, hopelessness, and pessimism. Beck's work, based on his astute clinical observations with depressed adults revealing negative thoughts of the self, world, and future, led to his ground-breaking book on cognitive therapy (Beck, 1967) and initial theorizing focusing on etiology and treatment approaches involving cognitive schemas, content, and process in depression. About this same time, Albert Ellis was promoting his cognitive approach called rational emotive behavior therapy (Ellis, 1957). Also about this time, an instrumental theoretical and empirical figure, Bandura, was advancing beyond psychoanalytic doctrine and was initiating his classic line of inquiry investigating behavioral (e.g., Bandura et al., 1961), and what ultimately became social-cognitive (e.g., Bandura, 1977), processes using a more experimental approach.

Progressing firmly as the cognitive revolution was in full swing, several theoretical advances in clinical cognitive understanding of psychopathology unfolded with an emphasis on cognitive products. Building on the basic behavioral understanding of learned helplessness approaches to human depression (Miller & Seligman, 1975), Abramson and colleagues underscored how attributions can affect depression (e.g., Abramson et al., 1978). Dodge and colleagues also applied attributional models to explicate aggression and conduct disorder (e.g., Crick & Dodge, 1994; Dodge, 1980).

About this same time, various experimental cognitive scientists were conducting more controlled experiments with core cognitive processes, including attention, memory, and executive functioning, using between groups comparison designs, sometimes with psychopathologically disordered groups. Relatedly, other experimentalists, using more social psychology and emotion traditions (e.g., Gross & Thompson, 2007) were similarly investigating cognitive processes and information processing, using experimental tasks developed in cognitive psychology, with clinical applications in aggression, anxiety, and mood (Joormann, 2010). At the present time, the state of the field is focused on integrating cognitive processes and products with either genetic influences or neuroscientific principles and findings (e.g., Beck, 2008; Disner, Beevers, Haigh, & Beck, 2011; Nigg & Casey, 2005).

Logical Models

Before initiating our review of cognitive processes and products in common psychopathologies, it is important to discuss several ways that can be used to more formally model the relationship between cognitive factors and psychopathology. The following section will discuss several logical models that could be used to conceptualize the role of cognitive influences in developmental psychopathology: correlate, consequence, risk factor/vulnerability, and causal risk factor. We draw on prior work articulating logical models that can more formally describe relations between a risk and psychopathology (e.g., Kazdin,

Kraemer, Kessler, Kupfer, & Offord, 1997; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). As we discuss later, a general shortcoming of the broad field of cognitive risks in developmental psychopathology across the life span is the lack of consideration and application of such logical models to more formally organize cognitive risks and try to rule out, or in, particular models based on the evidence. This is a goal of the chapter and our review. In addition, this section will also describe how cognitive factors might work together with other influences to contribute to psychopathology through the following mechanisms: moderation, mediation, and dynamic/transactional.

The simplest type of relationship characterizes a cognitive factor as a *correlate* of psychopathology, in that the two are associated (Kazdin et al., 1997). In addition, cognitive influences may also be a *consequence* of maladjustment, such that they accompany or follow directly from psychopathology. Correlates can be identified using cross sectional or retrospective study designs. Establishing cognitive correlates of mental health outcomes can act as the first step to inform future research designs, as discussed later, which are better able to address the temporal or potential causal relationship among cognitive influences and developmental trajectories of psychopathologies.

Within the conceptualization of a correlate, a cognitive construct may also act as a risk factor, or vulnerability, to psychopathology, such that the cognitive influence is associated with an increase in the probability of the outcome over the population base rate of the outcome (Kazdin et al., 1997). A risk factor is therefore a specific type of correlate that must temporally precede the outcome. Risk factors can be identified using only a prospective longitudinal design. Within risk factors, there are two categories: variable and fixed risk factors. Variable risk factors may change within an individual (e.g., age, height), whereas fixed risk factors do not change (e.g., race, sex). Cognitive influences are mutable variables, and therefore fall under the category of variable risk factors. For example and as we review later, a body of research that has utilized multiple time point designs has found that a negative inferential style predicts, especially in interaction with stressors, depression. In addition, as discussed in the literature review, prospective longitudinal studies suggest that impairments in EF, memory, attention and related brain systems predict later psychosis, ADHD, and PTSD, suggesting that cognitive deficits may be a risk factor for many disorders. A recent, relatively specific type of risk factor is an endophenotype (Gottesman & Gould, 2003), which is an intermediate trait (e.g., cognitive products and processes) that is relatively stable over time (e.g., present even during remission from illness) and present in healthy family members, thus linking genetic risk to later psychopathology.

Finally, a subset of risk factors may act as causal risk factors, such that the manipulation of these risk factors changes the probability of the outcome (Kazdin et al., 1997). The only study designs that are sufficient to identify causal risk factors include naturalistic experiments, laboratory experiments (e.g., randomized control trials, animal studies), or studies that examine dose-response relationships. Studies that have manipulated cognitive reappraisal in a laboratory setting, for instance, have demonstrated that this cognitive construct is associated with less sadness and general negative affect among both clinical and nonclinical participants (Perry & Henry, 2012). Likewise, training to reduce attentional bias toward negative information has been shown to reduce risk for depression recurrence (e.g., Browning, Holmes, Charles, Cowen, & Harmer, 2012), and experimental modification of cognitive emotion recognition at the perceptual level reduced anger and aggression in ambiguous contexts (Penton-Voak et al., 2013).

As part of a developmental, interdisciplinary approach to the study of cognitive risks to psychopathology, it is safe to assume that cognitive risk factors do not operate in isolation, but rather work together with other influences to engender risk to psychopathology. One possibility is moderation. In this type of relationship, a moderator B changes the relationship between independent variable A and the outcome O (Kraemer et al., 2001). It is important to note that, strictly speaking, the moderator B does not affect the level of A or the probability of A. Statistical analysis that examines moderators may seek to evaluate hypotheses of differential susceptibility to psychopathology as well as resiliency that buffers against these maladaptive outcomes.

A second mechanism that models how risk factors work together is mediation. In this type of relationship, a mediator B is caused to vary by the independent variable A. B, in turn, causes variation in the outcome O (Kraemer et al., 2001). Therefore, unlike in moderation, A does indeed affect the mediator B. Statistical analysis that examines mediators may seek to identify an intermediate variable in the causal pathway from A to a negative mental health outcome, thereby explaining how and why A influences that outcome.

A final model that explains how risk factors work together is the transactional model (e.g., Sameroff, 1975). In this model, variables are recursive, such that variables can serve both as an antecedent and as an outcome. For example, in the cognitive vulnerability-transactional stress model for depression (Hankin & Abramson, 2001),

a negative life event contributes to initial elevations in negative affect (e.g., sadness, anger), which interacts with cognitive risk factors (e.g., negative cognitive style) to maintain and amplify negative affect, thereby increasing risk for depression, which in turn contributes to future dependent negative life events (e.g., fight with a friend), perpetuating this recursive cycle. It is important to note that these logical models are not mutually exclusive. Indeed, it is highly likely that different models will hold true for different cognitive products and processes, or even for the same cognitive process or product at different times or for different individuals.

Overview and Plan for the Literature Review

The following sections review the evidence of core cognitive risks to psychopathology. There are several initial points to highlight. First, we do not review every single cognitive risk (process or product) that has ever been investigated. Rather, we concentrate this review on the main theoretically specified and empirically investigated factors and processes. Second, we do not review all forms of psychopathology, but rather focus on several of the most investigated and prevalent forms of psychopathologies—depression, BD, schizophrenia, anxiety (primarily posttraumatic stress disorder (PTSD), social anxiety disorder (SAD), generalized anxiety disorder (GAD), panic, and obsessive compulsive disorder (OCD), and externalizing disorders (primarily ADHD) and conduct disorders). Third, we organize this review mainly around prior reviews and meta-analyses, as well as essential individual papers that establish associations between these cognitive influences and those selective psychopathologies. It is important to emphasize, as became evident in conducting this review of core cognitive risks and psychopathologies, that not all of the cognitive products and processes have been studied with all of the main psychopathological disorders we reviewed. As such, our review covers associations between cognitive risks and psychopathology for those links for which there is a sufficient evidence base.

From this review, certain general conclusions can be reached that illustrate well-established principles of developmental psychopathology (see Cicchetti & Toth, 2009). First, it is clear that a variety of cognitive processes and products are linked to each of the psychopathologies reviewed here, thus reflecting the idea that there are multiple cognitive pathways to a given disorder (i.e., equifinality; Cicchetti & Toth, 2009). For example, research has linked both cognitive processes (e.g., deficits in executive functioning, biased attention for negative information) as well as cognitive products (e.g., negative inferential style, rumination) to depression. Additionally, evidence is consistent with the view that cognitive processes are perturbed across disorders (i.e., multifinality; Cicchetti & Toth, 2009), whereas cognitive products may operate as relatively more specific risks to particular psychopathologies based on the content and affective tone of the cognition and disorder. Still, this relatively broad conclusion requires additional research to substantiate, and it is a point to which we return to and expand upon later in the Discussion. For example, while the data suggest many processes may be relatively general risks to psychopathology transdiagnostically, future research may find greater specificity in cognitive processes when examined in greater detail (e.g., different neurotransmitter systems implicated in the underlying neural processes, or different strategies employed in cognitive tasks assessing these core processes). Likewise, seemingly specific cognitive products (e.g., rumination and worry) may share common underlying processes.

Second, the data reveal significant associations between cognitive risks and psychopathology, but the current state of knowledge is not consistently and systematically organized around the logical conceptual models presented in the previous section. To the extent possible, we present the evidence in this review in a manner that attempts to adjudicate among these potential logical models. Can certain ones be ruled out (e.g., purely concomitant association) for certain cognitive risks and particular forms of psychopathology? Are other models (e.g., risk factor/vulnerability) presently more favored and supported by the evidence?

Third, throughout the review we will point out the age group of the samples (e.g., child, adolescent, adult), some basic design features (e.g., cross sectional, longitudinal; case-control), and methods (e.g., questionnaires/self-reports in much of the product literature; cognitive tasks in most of the process studies). From the review it became clear that the majority of the work has focused on adult samples, although this generality varies and depends on the particular cognitive process and product investigated along with disorder. Research on cognitive processes and products that was conducted at different ages and developmental stages (e.g., infancy, childhood, adolescence, adulthood) with prospective longitudinal study designs can help to determine the developmental trajectories of these cognitive constructs, including emergence, stabilization, and change over time. For example, research has found that hostile attribution bias, a cognitive product linked to conduct disorder, is negatively associated with age (Orobio de Castro, Veerman, Koops, Bosch, & Monshouwer, 2002). We return to discuss and comment

on developmental/age features and design considerations later in the chapter.

A final key theme that emerged from this review is that there has generally been an independent, silo approach underlying inquiries into cognitive risks to development of psychopathology, as opposed to a more integrative approach across multiple levels of analysis (Cicchetti & Toth, 2009). To our knowledge no prior review has covered both cognitive products and processes together and development of several main psychopathologies, including both internalizing and externalizing problems. Many investigators focus on one product or process and one disorder only, and there has been little connection across multiple levels of analysis in cognition (i.e., lack of process and product integration) and across different forms of psychopathology (i.e., possibly transdiagnostic vs. specific disorder prediction). Just as young children interact together in parallel play, there has not been much cross talk between the cognitive products and process literature, or between literatures on cognition in different clinical disorders. Cognitive constructs at different levels inevitably constrain and influence one another in a bidirectional, transactional manner (Cicchetti & Toth, 2009), so future research should examine more than just one construct in isolation. For instance, cognitive theories of depression have begun to link deficits in inhibition with repetitive negative thought in depression (e.g., Zetsche, Avanzato, & Joormann, 2012). We organized our review by cognitive processes and products, rather than by clinical disorder, purposefully to begin to facilitate this conceptual shift focused on cognitive influences, which may be transdiagnostic risks to development of psychopathologies. We hope that this review will stimulate future research to move beyond the current silo approach and begin to integrate studies across cognitive products and processes and examine how these multiple cognitive influences predict development of several psychopathologies.

COGNITIVE PROCESSES

Executive Function

Executive function (EF) processes enable us to respond flexibly to the environment and regulate our thoughts and behaviors, allowing us to break out of habits, make decisions and evaluate risks, plan for the future, prioritize and sequence our actions, and cope with novel situations. EF is composed of a set of cognitive control processes, mainly supported by the prefrontal cortex (PFC), which regulate lower level cognitive processes (e.g., perception, motor responses) and thus enable self-directed behavior toward a goal (e.g., Miyake & Friedman, 2012). Given the breadth of the EF construct, many different tasks have been used to assess EF in the laboratory (Table 8.1). EF appears to be especially vulnerable to disruption, as evidenced by EF impairments associated with most forms of psychopathology, as discussed below. Thus, it has been proposed that EF deficits may be transdiagnostic intermediate phenotypes or risk factors for emotional, behavioral, and psychotic disorders (Susan Nolen-Hoeksema & Watkins, 2011). There is strong evidence that multiple aspects of EF are indeed impaired across most diagnostic groups, although the magnitudes of these deficits vary, both across disorders and across aspects of EF.

Core Components of EF: Shifting, Updating, and Inhibition

EF is best characterized as consisting of separable but related cognitive processes, with both unique and shared individual differences, genetic influences, and neural substrates (Miyake & Friedman, 2012). One influential model which has been applied to understanding the effects of psychopathology on EF, the *unity/diversity model*, has identified three fundamental aspects of EF: (1) shifting, (2) inhibition, and (3) updating working memory, as well as a common EF ability which is involved in all aspects of EF and may subsume inhibition (Miyake & Friedman, 2012). Shifting is defined as switching between task sets or response rules. For example, you may need to shift from reading this chapter to responding to an urgent email and back again. Inhibition is defined as suppressing or resisting a prepotent (automatic) response to make a less automatic but task-relevant response. For example, you may want to want to resist the automatic response of checking those not-so-urgent emails to complete reading the chapter. Updating is defined as monitoring and coding incoming information for task-relevance, and replacing no longer relevant information with newer, more relevant information. For example, as you read this chapter, you may be monitoring for a relevant piece of information you are looking for (say, the definition of updating), hold this information in working memory while you write it down, then replace it with the next relevant piece of information. Common EF is defined as what is shared across all EF tasks, and is posited to be the ability to monitor for and maintain goal and context information (e.g., the goal of finishing this section of the chapter; Miyake & Friedman, 2012). This theory is compatible with the view that the central role of the frontal lobes is active maintenance of goals, plans and other task-relevant information,

TABLE 8.1 Examples of Commonly Used EF Tasks

Construct	Task	Description	Outcome measure(s)	Methods citation[1]
Shifting	Intradimensional–extradimensional shift	Learn from feedback to select a stimulus based on one dimension, switch to the previously nonrewarded stimulus (intradimensional shift), then to a different stimulus dimension (extradimensional shift)	**1.** Perseverative errors in intradimensional and extradimensional shifts **2.** # of shifts achieved **3.** Time to complete	Robbins et al. (1998)
	Trail Making B[2]	Alternately connect letters and numbers in sequence (e.g., A-1-B-2) Often compared with Trail Making A (connect letters or numbers only, does not require shifting)	**1.** Trail Making B–Trail Making A time **2.** Errors in B **3.** Time to complete B	Strauss, Sherman, and Spreen (2006)
	Object Alternation	Find object hidden alternately under two different cups	Errors	Kuelz, Riemann, Zahn, and Voderholzer (2004)
	Wisconsin Card Sorting Task (WCST)	Learn from feedback to sort cards by one dimension (e.g., color), and then switch to a different dimension (e.g., shape) when given negative feedback on the first dimension (repeats with multiple sorting rules)	**1.** Perseverative errors **2.** # of rules achieved **3.** Time to complete	Strauss et al. (2006)
	Cued task switching	Perform one of two tasks depending on cue before each trial (e.g., color/shape, addition/subtraction, number/letter, categorize by size/categorize by living vs. nonliving)	**1.** Switch cost (switch–repeat RT) **2.** Perseverative errors	Friedman et al. (2008)
Inhibition	Color-word Stroop (experimental version)	Identify the color ink a color word is printed in; trials are incongruent (e.g., red written in blue ink) and congruent (e.g., red written in red ink) or neutral (noncolor word); trial types are randomly intermixed	**1.** Stroop interference (incongruent–neutral RT) **2.** Incongruent–neutral errors	Silton et al. (2010)
	Color-word Stroop (neuropsychological version)	Separate blocks of word reading, color naming, and incongruent (e.g., red written in blue ink) trials	**1.** Incongruent–color naming time **2.** Incongruent block time **3.** Incongruent block errors	Strauss et al. (2006)
	Stop-signal	Quickly categorize and respond to stimuli (e.g., left and right pointing arrows), unless a stop signal appears, signaling to withhold a response	**1.** Stop signal RT (time needed to stop a response) **2.** Commission errors	Band, Van der Molen, and Logan (2003)
	Antisaccade	Look in the opposite direction of visual cue	Errors (detected by eye tracking or failure to detect briefly presented target on correct side)	Friedman et al. (2008)
	Go/No-Go	Quickly categorize and respond to some stimuli and withhold a response to other stimuli	Commission errors	Rubia et al. (2001)
	Hayling	Read sentences where the final word is omitted but highly predictable; first complete sentences correctly (Part A), then with an unrelated word (part B)	**1.** Part B–Part A RT **2.** Part B errors	Strauss et al. (2006)
Working memory updating	Keep Track	Remember last exemplar word presented in several target categories and report these words at the end of the trial	Accuracy	Friedman et al. (2008)
	Letter Memory	Remember and repeat the last three letters in a letter string, adding the most recent letter and dropping the 4th letter back	Accuracy	Friedman et al. (2008)
	Verbal n-back	Indicate if the stimulus (usually letter) matches the stimulus *n* (e.g., 3) items back	Accuracy	Braver, Cohen, Nystrom, Jonides, and Smith (1997)
	Spatial n-back	Indicate if the spatial location of a stimulus matches the location *n* (e.g., 3) items back	Accuracy	Friedman et al. (2008)

(*continued*)

TABLE 8.1 (*Continued*)

Construct	Task	Description	Outcome measure(s)	Methods citation[1]
Visuospatial working memory	Corsi block tapping/ Spatial Span	Tap irregularly arranged blocks/squares in the same order as experimenter (Corsi blocks) or computer (Spatial Span).	Span (max. length of sequence correctly performed)	Strauss et al. (2006)
	Self-Ordered Pointing	Search an array of boxes for hidden tokens; token is only in each location once	**1.** Errors (return to previous location) **2.** Strategy score (how often search is initiated from same starting box)	Owen, Downes, Sahakian, Polkey, and Robbins (1990)
	Sequential Comparison	View an array of colored squares and after a delay, indicate if any squares have changed colors in a test array	Span (see reference)	Luck and Vogel (1997)
Verbal working memory	Digit Span (Forward and Backward)	Repeat sequence of numbers in forward or reverse order	Span (max. length of sequence correctly performed)	Strauss et al. (2006)
	Letter-Number Sequencing	Repeat list of alternating letters and numbers, resequenced into numbers first, then letters	Span (max. length of sequence correctly performed)	Strauss et al. (2006)
	Reading Span	Read a serious of unrelated sentences, then recall the last word of each sentence.	# correctly recalled words	Friedman and Miyake (2004)
	Operation Span	Read aloud and verify simple math equations, then read aloud a presented word; at end of trial, recall all words	# correctly recalled words	Miyake et al. (2000)
Verbal fluency	Semantic Verbal Fluency/Category Fluency	Say as many words from a semantic category (e.g., animals) as possible in 1 (or 3) min	**1.** Switches between subcategories **2.** # of words	Troyer, Moscovitch, and Winocur (1997)
	Phonemic Verbal Fluency/Controlled Oral Word Association (COWA)	Say as many items starting with a certain letter (usually F, A, S) as possible in 1 (or 3) min	# of words	Troyer et al. (1997)

[1]Citations are for sources that provide a full description of the task and outcome measures of the most recent or recommended version of the task, not necessarily the first publication to report the task.
[2]Not recommended for future research because it has poor construct validity (e.g., effect sizes are equal for the Trail Making Test Part A measures; Snyder, 2013).

which may be essential for all aspects of EF (Miller & Cohen, 2001).

The largest deficits on these core aspects of EF are found for individuals with schizophrenia. Meta-analyses have found large impairments on measures of shifting, inhibition, and updating (Table 8.2). A recent meta-analysis also found that adolescents with psychosis risk syndrome have small but significant deficits in EF, which are somewhat larger in those who go on to convert to schizophrenia (Giuliano et al., 2012). EF deficits increase during the prodrome, and increase again with the first psychotic episode, then appear to be fairly stable over time (e.g., see Lewandowski, Cohen, & Ongur, 2011 for review), with little evidence that individuals with schizophrenia experience greater age-related declines in EF than healthy individuals (Irani, Kalkstein, Moberg, & Moberg, 2011). However, there is some evidence that EF deficits are sensitive to symptom levels. Specifically, EF impairments in schizophrenia are associated with negative symptoms and disorganization, but not with positive symptoms (Dibben, Rice, Laws, & McKenna, 2009).

These EF processes are also impaired in individuals with mood disorders, although the magnitude of these deficits is somewhat smaller than those in schizophrenia. Meta-analytic evidence demonstrates that individuals with depression are significantly impaired on measures tapping shifting, inhibition, and updating, with medium effect sizes, while individuals with BD have somewhat larger impairments in shifting and inhibition, while there is little research on updating in individuals with BD (Table 8.2). More research is needed to determine how EF deficits change over the life span in individuals with depression and BD. A meta-analysis of children with BD found fairly comparable effect sizes to those in adults (Walshaw, Alloy, & Sabb, 2010), suggesting that EF deficits are already present early in BD and may be relatively stable across the life span. EF deficits in individuals with depression appear to be relatively stable from adolescence through older adulthood (Snyder, 2013), but there has been little research in younger adolescents or children with depression. EF deficits in BD and depression also appear to be fairly stable across current mood state, as most measures of EF

TABLE 8.2 Summary of Recent EF Meta-Analyses[1]

	Meta-analysis	Clinical group	Shifting	Inhibition	Updating	Verbal WM manip.	Verbal WM maint.	Visuospatial WM	Phonemic VF	Semantic VF	Planning
Depression	Rock, Roiser, Riedel, and Blackwell (2013)	MDD	0.44	–	–	–	–	0.45	–	–	0.43
	Snyder (2013)	MDD	0.47	0.58	0.57	0.52	0.39	0.45	0.46	0.70	0.38
Average			**0.46**	**0.58**	**0.57**	**0.52**	**0.39**	**0.45**	**0.46**	**0.70**	**0.41**
BD	Arts, Jabben, Krabbendam, and Van Os (2008)	Euthymic BD (all)	0.94	0.73		1.02	0.37	–	0.59	0.87	–
	Bora, Yucel, and Pantelis (2009)	Euthymic BD (all)	0.78	0.76		0.75	0.37	–	0.60	–	–
	Bora, Yücel, Pantelis, and Berk (2011)	Euthymic BD II	0.51	0.72		–	0.39	–	0.47	0.46	0.29
	Kurtz and Gerraty (2009)	Euthymic BD (all)	0.67	0.75		0.65	0.41	–	0.51	0.75	_
	Kurtz and Gerraty (2009)	Manic/ mixed BD (all)	0.68	–	–	–	–	–	0.51	0.59	_
	Kurtz and Gerraty (2009)	Depressed BD (all)	0.64	–	–	–	_	_	0.93	_	_
	Mann Wrobel, Carreno, and Dickinson (2011)	Euthymic BD (all)	0.73	0.78		0.81	0.40	0.55	0.55	0.58	_
	Robinson et al. (2006)	Euthymic BD (all)	0.77	0.63		0.98	0.47	–	0.34	1.09	_
	Torres, Boudreau, and Yatham (2007)	Euthymic BD (all)	0.62	0.71		0.54	–	–	–	–	_
	Walshaw et al. (2010)	Pediatric BD (all)	0.73	0.46		–	–	0.80	0.34	0.38	0.96
Average			**0.71**	**0.69**	–	**0.79**	**0.40**	**0.68**	**0.54**	**0.67**	**0.63**
OCD	Abramovitch, Abramowitz, and Mittelman (2013)	OCD	0.52[2]	0.49	–	0.34[3]		0.37[3]	–	–	0.44
	Shin, Lee, Kim, and Kwon (2013)	OCD	0.42	0.55	–	0.11		0.49	0.39	0.42	0.73
	Snyder et al. (2015)	OCD	0.50	0.37	0.71	0.31	0.07	0.47	0.39	0.34	0.44
Average			**0.48**	**0.47**	**0.71**	**0.22**		**0.44**	**0.39**	**0.41**	**0.54**
PTSD	Polak et al. (2012)	PTSD vs. trauma exposed controls	0.70	0.10	–	0.45	–	–	–	–	–
Schizophrenia	Bokat and Goldberg (2003)	Schizophrenia	–	–	–	–	–	–	0.99	1.27	–
	Dickinson, Ramsey, and Gold (2007)	Schizophrenia	0.87	0.99	–	0.86	0.73	–	0.83	1.41	–
	Doughty and Done (2009)	Schizophrenia	–	–	–	–	–	–	–	1.34	–
	Forbes, Carrick, McIntosh, and Lawrie (2009)	Schizophrenia	–	–	–	1.08	0.82	0.87	–		–
	Henry and Crawford (2005)	Schizophrenia	0.98	0.98	–	–	–	–	0.95	1.12	–
	Mesholam-Gately, Giuliano, Goff, Faraone, and Seidman (2009)	First episode psychosis	0.86	0.88	–	0.79	0.50	0.80	0.69	1.24	–
	Piskulic, Olver, Norman, and Maruff (2007)	Schizophrenia	–	–	0.83	–	–	1.09	–	–	–
	Stefanopoulou et al. (2009)	Schizophrenia	0.99	–	–	–	–	–	1.03	–	–

(*continued*)

TABLE 8.2 (*Continued*)

	Meta-analysis	Clinical group	Shifting	Inhibition		Updating	Verbal WM manip.	Verbal WM maint.	Visuospatial WM	Phonemic VF	Semantic VF	Planning
Average ADHD			**0.92**	**0.95** Stroop	Motor	**0.83**	**0.91**	**0.68**	**0.92**	**0.90**	**1.28**	–
	Alderson, Rapport, and Kofler (2007)	ADHD children and adolescents		–	0.63	–	–	–	–	–	–	–
	Bálint et al. (2009)	ADHD adults	0.72	0.30	–	–	–	–	–	–	–	–
	Boonstra et al. (2005)	ADHD adults	0.65	0.13	–	–	0.44	0.29	–	0.62	–	–
	Frazier, Demaree, and Youngstrom (2004)	ADHD all ages	0.50	0.56	0.54	–	–	–	–	0.46	0.41	–
	Hervey, Epstein, and Curry (2004)	ADHD adults	–	0.15	–	–	–	–	–	–	–	–
	Lansbergen, Kenemans, and Van Engeland (2007)	ADHD adults	–	0.24	–	–	–	–	–	–	–	–
	Lijffijt, Kenemans, Verbaten, and Van Engeland (2005)	ADHD adults	–	–	0.58	–	–	–	–	–	–	–
	Van Mourik, Oosterlaan, and Sergeant (2005)	ADHD all ages	–	0.35	–	–	–	–	–	–	–	–
	Walshaw et al. (2010)	ADHD children and adolescents	0.37	0.38	0.63	–	0.63	–	0.86	0.68	0.38	0.38
	Willcutt, Doyle, Nigg, Faraone, and Pennington(2005)	ADHD children and adolescents	0.51	–	0.61	–	0.55	–	0.63	–	–	0.60
Average (all ages)			**0.55**	**0.30**	**0.63**	–	**0.54**	**0.29**	**0.75**	**0.59**	**0.41**	**0.49**
Children and adolescents only			**0.44**	**0.23**	**0.61**	–	**0.59**	–	**0.75**	**0.68**	**0.38**	**0.49**
Adults only			**0.69**	**0.38**	**0.79**	–	**0.44**	**0.29**	–	**0.62**	–	–

[1] Summary of meta-analyses conducted in the last ten years. Weighted mean effect size (Cohen's *d*) comparing healthy control participants to the clinical group. All effect sizes have been recoded such that positive values represent worse task performance by the clinical group. When a meta-analysis reported effect sizes for multiple individual tasks within an EF component, the average of these effect sizes is reported.

[2] Composite measures including some tasks we would not classify as shifting (verbal fluency, design fluency, and WAIS similarities) in addition to traditional shifting tasks.

[3] Includes updating tasks.

Manip. = manipulation. Maint. = maintenance. VF = verbal fluency.

remain equally impaired in euthymic individuals with BD (Kurtz & Gerraty, 2009; Table 8.2) and individuals with depression in remission (Snyder, 2013). On the other hand, some EF deficits increase with symptom severity (e.g., see McDermott & Ebmeier, 2009 for meta-analysis). However, longitudinal research is needed to determine whether EF tracks changes in depression severity, or whether preexisting EF abilities affect depression severity. Preliminary evidence suggests that the latter may be the case: individuals who had more severe EF (shifting/inhibition) deficits during their first MDD episode were more likely to relapse within a year (Schmid & Hammar, 2013).

Individuals with OCD have impaired performance across these core EF domains, with small effect sizes for shifting and inhibition, but large effect sizes for updating (Table 8.2). Importantly, while depression frequently co-occurs with OCD, EF deficits in OCD are not driven by co-occurring depression, as even those with low levels of depressive symptoms show the same level of EF deficits (Snyder, Kaiser, Warren, & Heller, 2015). While there have been few studies of EF in children and adolescents with OCD, they appear to have EF deficits similar to those of adults with OCD (e.g., Andrés et al., 2007; Shin et al., 2008), suggesting that EF deficits are present from soon after illness onset. EF deficits appear to be fairly stable through adulthood (Snyder et al., 2015), but there has been little research on older adults with OCD.

Evidence for impairments in these core EF domains is less consistent for other anxiety disorders. A recent meta-analysis found that compared with trauma-exposed individuals who did not develop PTSD, individuals with PTSD had worse performance on measures of shifting, with a medium effect size, but not the Stroop measure of inhibition (Table 8.2; Polak, Witteveen, Reitsma, & Olff, 2012). However, a review of the literature including a wider range of inhibition tasks suggests that individuals with PTSD do experience inhibition deficits (Aupperle, Melrose, Stein, & Paulus, 2012). EF impairments in individuals with PTSD do not seem to be clearly influenced by current mood state, suggesting that they are trait-like (Aupperle et al., 2012). However, unlike OCD, co-occurring depression may account for EF deficits in individuals with PTSD, although more research in individuals without severe depressive symptoms is needed to confirm this finding (Polak et al., 2012). While most research has focused on adults, a few studies in children and adolescents have also found EF impairments associated with trauma and PTSD (Carrion, Wong, & Kletter, 2012). However, in adults there is some evidence that EF deficits associated with PTSD increase with age from early to middle adulthood, although this finding is based on cross sectional studies, leaving the possibility that cohort effects (e.g., in type of trauma exposure) could account for these findings (Polak et al., 2012).

In contrast with OCD and PTSD, there is not strong evidence for broad EF impairments associated with other anxiety disorders, and there have been no published meta-analyses. While a few studies have found impairments in shifting associated with PD, SAD and GAD in adults (Airaksinen, Larsson, & Forsell, 2005; Cohen et al., 1996; Mantella et al., 2007), others have found no evidence of impairment in shifting (Airaksinen et al., 2005; Boldrini et al., 2005; Purcell, Maruff, Kyrios, & Pantelis, 1998), or inhibition (Price & Mohlman, 2007a; van den Heuvel et al., 2005; Van der Linden, Ceschi, Zermatten, Dunker, & Perroud, 2005). In sum, there is limited and inconsistent evidence for EF impairments on traditional neuropsychological tasks in individuals with anxiety disorders other than OCD and PTSD.

However, research in nonclinical samples suggests that trait anxiety, and especially anxious apprehension (worry) is associated with impairments in a specific aspect of EF, inhibiting competing responses. A number of studies have found that high trait anxiety is associated with impaired inhibition task performance (e.g., Bishop, 2008; Eysenck & Derakshan, 2011; Snyder et al., 2010), although others have not (e.g., Avila & Parcet, 2001), likely due to differences in the types of tasks, and potentially most critically, the measures of anxiety used. Recent research suggests that anxious apprehension, but not anxious arousal, is associated with an impaired ability to inhibit competing verbal responses (Snyder et al., 2010). Since anxious apprehension and anxious arousal can both be present to different degrees in individuals with anxiety disorders, more specific measures of anxious apprehension, as well as more sensitive and specific measures of inhibition, may be beneficial in detecting EF deficits in such individuals.

Finally, ADHD is associated with impairments in shifting and inhibition, while updating has not been widely studied. While earlier theories posited a core inhibitory deficit that secondarily disrupts other aspects of EF (e.g., Barkley, 1997), recent meta-analyses demonstrate that only motor response inhibition tasks (stop signal and go/no-go) show substantial deficits, while the Stroop measure of inhibition shows only a small effect size (Table 8.2). EF is also impaired in other externalizing disorders, including ODD/CD, but these deficits may be accounted for at least in part by co-occurring ADHD (see Ogilvie, Stewart, Chan, & Shum, 2011 for meta-analysis). EF deficits occur in individuals of all ages with ADHD,

from preschoolers (Pauli-Pott & Becker, 2011) through mid-adulthood (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005). However, effect sizes are somewhat larger in meta-analyses of adults with ADHD than those with children and adolescents (Table 8.2). It is possible that the subset of individuals who continue to experience ADHD symptoms into adulthood have a more severe form of the disorder, contributing to greater EF deficits, or that poor EF is a risk factor for continued ADHD symptoms in adulthood. However, this must be interpreted with caution because different tasks or task variants are often used with different age ranges, precluding direct comparisons.

Working Memory

While shifting, inhibition, and updating are important aspects of EF, this model in no way posits that these are the only components of EF. For example, working memory is often considered a component of EF. Working memory (WM) is defined as actively maintaining (i.e., 'holding on line') or manipulating information across a short delay. Manipulating information in WM places heavier demands on EF (i.e., the *central executive* component of WM) than simple maintenance (Repovs & Baddeley, 2006). WM maintenance can further be divided into verbal (e.g., words, letters, and numbers) and visuospatial (e.g., shapes, patterns, and spatial locations) stores), while the central executive component of WM is believed to be domain-general (e.g., Repovs & Baddeley, 2006).

Working memory deficits are widespread across forms of psychopathology, but vary in magnitude both across disorders and across components of WM. Visuospatial WM is consistently impaired, with large effect sizes for individuals with schizophrenia, and medium-small effect sizes for BD and ADHD, and small but significant effect sizes for depression and OCD (children and adolescents for ADHD, mainly adults for all other disorders; Table 8.2). Verbal WM is also widely impaired, but deficits are smaller for simple verbal working memory maintenance (e.g., digit span forward) than verbal working memory manipulation (e.g., digit span backward). Specifically, meta-analyses show verbal WM manipulation deficits with large effect sizes for schizophrenia, medium effect sizes for BD, MDD, and ADHD (somewhat larger for children/adolescents than adults), and small but significant effect sizes for PTSD and OCD. In contrast, simple verbal WM maintenance tasks show only medium effect sizes for schizophrenia, small effects for BD, depression, and ADHD (only adults meta-analyzed), and no significant impairment in OCD (Table 8.2). There has been very little research on WM in individuals with anxiety disorders other than OCD, but there have been reports of impaired visuospatial WM in individuals with PD (Boldrini et al., 2005), and impaired verbal WM manipulation, but not maintenance, in individuals with GAD (Christopher & MacDonald, 2005).

The finding that manipulation is more impaired than maintenance, along with evidence that visuospatial and verbal WM manipulation are equally impaired, both support the view that working memory deficits in these disorders are due to impairment in the central executive aspect of working memory, rather than the content-specific maintenance systems (Barch, 2005). This suggests that verbal WM deficits may arise from difficulty with encoding and/or manipulating information in working memory, rather than maintenance of information. Supporting this, a meta-analysis found that working memory deficits associated with schizophrenia do not increase with the delay interval over which material must be maintained (Lee & Park, 2005), while studies have found that increasing presentation time or stimulus saliency to aid encoding improves working memory performance in individuals with schizophrenia (Lee & Park, 2005). However, this more fine-grained analysis of the factors driving WM impairments has not been performed for other forms of psychopathology.

Complex Tasks: Verbal Fluency and Planning

Many complex tasks may also tap multiple aspects of EF. For example, verbal fluency tasks (generating words starting with a certain letter or from a category) likely tap several cognitive processes (Rende, Ramsberger, & Miyake, 2002). Planning tasks are also complex, involving multiple cognitive demands (Goel & Grafman, 1995), and so may not represent a single EF ability. Notably, verbal fluency and planning tasks are frequently used in clinical studies. Such tasks may be commonly implemented in clinical research because they are viewed as more ecologically sensitive: the complexity of verbal fluency and planning tasks may make them more relatable to real-world tasks that require similar skills. Thus, there are both disadvantages (in terms of interpretability) and advantages (in terms of ecological validity) in the use of such complex EF tasks.

Deficits in verbal fluency are widespread across disorders. Indeed, meta-analyses show that the largest deficit for adults with schizophrenia and depression is found on the semantic verbal fluency task, with large and medium effect sizes respectively (Table 8.2). Semantic verbal fluency is also impaired in individuals with BD (all ages, with medium effect sizes), OCD (mainly adults, with small effect sizes), and ADHD (all ages, with small effect sizes), while there is

inconsistent evidence for verbal fluency in individuals with PTSD (Aupperle et al., 2012; Table 8.2). For schizophrenia, BD, and MDD, effect sizes for phonemic verbal fluency are somewhat smaller than those for semantic, although still significant (Table 8.2). In contrast, individuals with OCD have equal impairments in the two forms of verbal fluency, and verbal fluency deficits associated with ADHD appear to be larger for phonemic verbal fluency than semantic verbal fluency (Table 8.2). There has been little research on verbal fluency in anxiety disorders other than OCD: one study reported impaired phonemic verbal fluency in individuals with PD (Gladsjo et al., 1998), while others found no impairment in individuals with GAD (Airaksinen et al., 2005) or SAD (Hood et al., 2010). However, conclusions are premature given the paucity of evidence.

Why might semantic and phonemic verbal fluency tasks be differentially affected in different disorders? Verbal fluency tasks impose multiple EF demands (e.g., shifting among subcategories, monitoring for repeated words, memory retrieval). One possibility as to why semantic verbal fluency is more impaired in individuals with schizophrenia, BD, and depression is that it may place heavier demands on shifting, and particularly on selecting what to switch to, since category cues are likely to lead to the activation of many category members, which then compete for production (Snyder & Munakata, 2010). Another possibility is that deficits in semantic memory retrieval may contribute to semantic verbal fluency impairment, particularly in individuals with schizophrenia. For example, a meta-analysis found that individuals with schizophrenia have large deficits on semantic verbal fluency both for switching between subcategories, an index of EF ($d = 1.02$), and semantic clustering, and index of semantic memory ($d = 0.93$) (Doughty & Done, 2009). In contrast, the larger effect for phonemic verbal fluency in individuals with ADHD could potentially be due to deficits in phonological processing in many individuals with ADHD, since ADHD and reading disabilities frequently co-occur (Willcutt, Pennington, Olson, & DeFries, 2007). Thus, deficits in verbal fluency may arise from a variety of sources, and illustrate the difficulty of interpreting results from complex tasks.

Planning has been much less studied. Individuals with BD have significant impairments in planning, with one meta-analysis finding a small effect size in adults and another finding a large effect size in children and adolescents (Table 8.2). Adults with depression also have significant, but small, impairments on planning tasks (Table 8.2). In individuals with ADHD, two meta-analyses, both in children and adolescents, found quite different effect sizes for planning tasks, one small, one medium (Table 8.2). Likewise, two meta-analyses of individuals with OCD found different effect sizes for planning, two small and one medium (Table 8.2). Finally, there is inconsistent evidence for planning deficits associated with PTSD (Aupperle et al., 2012). Thus, while planning tasks in theory tap multiple aspects of EF, standard measures of planning may be less sensitive than other EF tasks in detecting more subtle EF deficits associated with some disorders.

Attention

What is attention? Despite William James's (1890) famous assertion that "everyone knows what attention is" (pp. 403–404), attention has been conceptualized and defined in many ways, and is best thought of as an umbrella term for a set of processes that filter incoming information and allocate processing resources, including *sustained attention, selective attention,* and *divided attention*. Problems with attention can arise either because there are deficits in attentional processes themselves (e.g., difficulty maintaining any attentional focus), or because attention is allocated in a way that is not adaptive (*attentional bias,* e.g., focusing on negative information). There is evidence for both attentional deficits and attentional biases associated with psychopathology, with the strongest evidence for attentional deficits in schizophrenia, bipolar disorder and ADHD, and attentional biases in depression and anxiety disorders.

Sustained Attention

Sustained attention or *vigilance* maintains alertness continuously over time. For example, sustained attention is what enables you to stay focused on reading this chapter instead of drifting off into a daydream. Sustained attention is usually measured with continuous performance tests (CPTs), in which a stream of stimuli must be monitored for several minutes to detect infrequent and nonsalient targets (e.g., a particular number sequence in a stream of numbers). Sustained attention involves subcortical brain systems that maintain basic arousal and alertness (e.g., reticular activating system), but also the frontoparietal cognitive control network that also supports EF. This is probably because sustaining attention on tasks like the CPT, while seemingly simple, requires EF processes such as maintaining the task goal and monitoring for task-relevant stimuli. Sustained attention is particularly impaired in individuals with schizophrenia, BD, and ADHD. In contrast, there is limited evidence for sustained attention impairments in individuals with depression or anxiety disorders.

Recent meta-analyses have found impairments with large deficits on sustained attention tasks for individuals with schizophrenia, medium deficits for individuals with BD and MDD, and small to medium deficits for individuals with OCD (Table 8.3). While most research has focused on adults, deficits in sustained attention have been reported in children and adolescents with schizophrenia (e.g., Groom et al., 2008; Thaden et al., 2006; but see Ueland, Øie, Inge Landrø, & Rund, 2004) and BD (Table 8.3). A recent meta-analysis also found that adolescents with psychosis risk syndrome have small but significant deficits in sustained attention, which are somewhat larger in those who go on to convert to schizophrenia (Giuliano et al., 2012). Sustained attention deficits appear to be relatively stable over the course of illness: they do not vary with age in individuals with schizophrenia through adulthood and older adulthood (Bozikas & Andreou, 2011; Irani et al., 2011), and persist during euthymia in individuals with BD (Table 8.3) and in remission for individuals with MDD (Rock et al., 2013).

As for EF, there is some evidence that sustained attention impairments may be risk markers for psychosis and BD. Adolescents scoring in the high-risk range on a questionnaire for psychotic-like experiences had impaired sustained attention (Kim et al., 2012). Furthermore, unaffected first-degree relatives of individuals with BD also have significant, though milder, deficits in sustained attention (Bora et al., 2009). On the other hand, there

TABLE 8.3 Summary of Recent Attention Meta-Analyses[1]

	Meta-analysis	Group	Sustained attention	Biased attention: dot-probe	Biased attention: emotional Stroop
Depression	Peckham et al. (2010)	MDD	–	0.70	0.16
	Epp et al. (2012)	MDD			0.24
	Rock et al. (2013)	MDD	0.65		
Average					**0.20**
BD	Arts et al. (2008)	Euthymic BD (all)	0.58		
	Bora et al. (2009)	Euthymic BD ((all)	0.83		
	Kurtz and Gerraty (2009)	Euthymic BD ((all)	0.69		
	Kurtz and Gerraty (2009)	Manic/mixed BD (all)	0.79		
	Robinson et al. (2006)	Euthymic BD (all)	0.60		
	Torres et al. (2007)	Euthymic BD (all)	0.74		
	Walshaw et al. (2010)	Pediatric BD (all, clinical status not specified)	0.40		
Average			**0.66**		
Anxiety Disorders	Bar-Haim et al. (2007)	OCD, GAD, PTSD, SAD, PD, and simple phobia	–	0.38	0.45
	Abramovitch et al. (2013)	OCD	0.50		
	Shin et al. (2013)	OCD	0.45		
Average			**0.48**		
Schizophrenia	Dickinson et al. (2007)	Schizophrenia	0.92		
	Mesholam-Gately et al. (2009)	First episode psychosis	0.71		
	Rajji, Ismail, and Mulsant (2009)	First episode schizophrenia	0.83		
	Rajji et al. (2009)	Youth-onset schizophrenia	0.73		
Average			**0.80**		
ADHD	Bálint et al. (2009)	Adults	0.55		
	Boonstra et al. (2005)	Adults	0.57		
	Frazier, Demaree, and Youngstrom (2004)	All ages	0.61		
	Hervey et al. (2004)	Adults	0.64		
	Huang-Pollock et al. (2012)	Children and adolescents	0.59		
	Pauli-Pott and Becker (2011)	Preschool Children	0.54		
	Schoechlin and Engel (2005)	Adults	0.52		
	Walshaw et al. (2010)	Children and adolescents	0.56		
	Willcutt et al. (2005)	Children and adolescents	0.58		
Children and adolescents only			0.57		
Adults only			0.57		
Average (all)			0.58		

[1]Summary of meta-analyses conducted in the last ten years. Weighted mean effect size (Cohen's *d*) comparing healthy control participants to the clinical group. All effect sizes have been recoded such that positive values represent worse task performance by the clinical group. When a meta-analysis reported effect sizes for multiple individual tasks within an attention component, the average of these effect sizes is reported.

is some evidence that sustained attention impairments develop over the course of psychotic illness: early-onset schizophrenia patients show a failure to improve performance on attention tasks during adolescence, while healthy adolescents do improve performance, suggesting that schizophrenia is associated with a failure in the developmental trajectory (Frangou, 2009).

Inattention symptoms obviously play a central role in ADHD. However, the diagnostic criteria for ADHD in the DSM-IV are not specifically defined in cognitive terms, and behaviors labeled as *inattentive* may not always arise from deficits in attentional processes per se (e.g., behavior labeled inattentive might be due to poor EF; Huang-Pollock, Nigg, & Carr, 2005). Nonetheless, some diagnostic criteria do appear to describe difficulty sustaining attention. Indeed, there is strong meta-analytic evidence that children, adolescents, and adults with ADHD all have impaired performance on laboratory sustained attention tasks, with equal effect sizes across ages, including preschool, suggesting that attentional processes are affected from early in development (Table 8.5). Specifically, individuals with ADHD discriminate between targets and distracters more slowly and less accurately, and show an increasing number of omission errors over time during task performance, consistent with difficulty sustaining attention, but do not show a bias to make more target responses which would be consistent with impulsive responding (Huang-Pollock, Karalunas, Tam, & Moore, 2012).

There is much less evidence for sustained attention impairments associated with anxiety disorders other than OCD, with mixed evidence of impairments in sustained attention associated with PTSD (e.g., Jenkins, Langlais, Delis, & Cohen, 2000; Vasterling et al., 2002, but see, e.g., LaGarde, Doyon, & Brunet, 2010; Twamley, Hami, & Stein, 2004), and no evidence of impairment in PD (e.g., Galderisi et al., 2008; Gladsjo et al., 1998).

Selective Attention

Selective attention filters incoming information to select relevant information for further processing. This selection can occur on the basis of sensory modality (e.g., pay attention to visual, not auditory, information), sensory attributes (e.g., look for something blue) or spatial locations (e.g., pay attention to the left side of space). (Selecting information on the basis of more abstract processes or goals is covered under executive function). For example, if you are reading this chapter in a busy coffee shop, selective attention enables you to attend to the words on the page while filtering out the conversations going on around you. Selective attention, especially in the visuospatial domain, is largely supported by the dorsal attention network (also called the orienting network), which consists of the posterior parietal cortex and frontal eye fields, and is involved in voluntary orienting of attention based on cues (e.g., Posner & Rothbart, 2007). Somewhat surprisingly given impairments in seemingly more basic sustained attention, selective attention deficits do not appear to be strongly associated with psychopathology, with the possible exception of auditory selective attention in individuals with schizophrenia.

There is some evidence that auditory selective attention may be impaired in individuals with schizophrenia. Specifically, several studies have found that adults with schizophrenia or schizotypal personality disorder were worse at selective attention in dichotic listening tasks, in which two different verbal stimuli are presented simultaneously, one in each ear, with instructions to identify the stimuli in only one ear (Egeland et al., 2003; Hugdahl et al., 2003; Voglmaier et al., 2009). However, these deficits may not be present in younger and stabilized patients (Løberg, Jørgensen, & Hugdahl, 2002).

Unlike auditory selective attention, there is not strong evidence for impairments in visuospatial selective attention associated with schizophrenia. While individuals with schizophrenia are slower overall on measures of selective attention, they generally perform as well as healthy control participants at excluding distracters from attention (Gold, Hahn, Strauss, & Waltz, 2009). Specifically, in Posner spatial cueing tasks, in which a visual cue indicates the probable location of an upcoming stimulus, individuals with schizophrenia are slower to respond overall, but benefit as much from valid cues, and are slowed as much by invalid cues, as healthy control participants (Gold et al., 2009). Similar findings have been reported for visual search tasks, in which targets of a certain shape and color, rather than spatial location, must be selectively focused on (for review, see Gold et al., 2009). Event related potential (ERP) evidence further suggests that individuals with schizophrenia are as fast as healthy participants to allocate attention to a target, even though their subsequent motor response is slowed (Luck et al., 2006).

Mirroring the findings in schizophrenia, there is not clear evidence for impaired visuospatial selective attention in individuals with ADHD despite impaired sustained attention. Specifically, while children with ADHD are slower to respond to cued targets, children with and without ADHD have a similar pattern of response slowing when distracters are present or cues are invalid (Friedman-Hill et al., 2010; Huang-Pollock et al., 2005). Meta-analytic

evidence suggests only small differences in cued visuospatial selective attention between children with ADHD and healthy children (d =0.22–0.27, (Huang-Pollock et al., 2005). This suggests that children with ADHD are not specifically impaired at visually selecting target items or locations. While there is some evidence that children and adults with ADHD have difficulty selectively attending to auditory information (Gomes et al., 2012; Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004), the possibility that these findings could also be due to general slowing rather than selective attention deficits per se requires further investigation.

Interestingly, there is some evidence that children and adults with ADHD do as well has healthy controls at filtering out distracters when task demands are high, but show deficits when task demands are low (easy target discrimination and low distracter salience), suggesting that individuals with ADHD may have trouble endogenously sustaining attention in easy tasks, rather than selective attention per se (Friedman-Hill et al., 2010). Thus, as in schizophrenia, it appears that individuals with ADHD may not have a core deficit in filtering irrelevant visual information, but rather problems with recruiting and sustaining attentional control. This view is consistent with the finding that individuals with ADHD are reliably impaired on sustained attention tasks, which are relatively undemanding and may therefore lead to more lapses in attention.

There has been little research on selective attention in other forms of psychopathology, with mixed reports of impaired and unimpaired selective attention in adults with depression (Egeland et al., 2003; Hammar, Kildal, & Schmid, 2012; Hugdahl et al., 2003, but see, e.g., Desseilles et al., 2009; Godard et al., 2011; Reppermund, Ising, Lucae, & Zihl, 2009), BD (Burdick et al., 2009), PTSD (Johnsen, Kanagaratnam, & Asbjørnsen, 2011, but see, e.g., Leskin & White, 2007; Vasterling et al., 2002) and OCD (Clayton, Richards, & Edwards, 1999), but only reports of unimpaired performance in PD (Clayton et al., 1999) and SAD (Sachs, Anderer, Doby, Saletu, & Dantendorfer, 2003). Furthermore, it is not clear if those deficits that have been reported might result from general slowing, as in schizophrenia and ADHD.

Divided Attention

Divided attention allocates processing resources to more than one task at once. To return to our coffee shop example, divided attention enables you to continue reading the chapter while at the same time listening for your order to be called. In the laboratory, divided attention is generally assessed with tasks that require dividing attention between two simple tasks at once (e.g., identifying visual and auditory targets). Coordinating two tasks in this way activates the frontoparietal cognitive control network, even when the individual tasks do not (Collette et al., 2005), suggesting that, like sustained attention, it places demands on EF.

There has been less research on divided attention than other forms of attention. However, those studies which have examined this domain found divided attention impairments in adults (e.g., Daban et al., 2005; Raffard & Bayard, 2012) and adolescents (Boutin, Gingras, & Rouleau, 2010) with schizophrenia, adults with BD (Godard et al., 2011), adults with depression (Godard et al., 2011; Reppermund et al., 2009), and both children/adolescents (e.g., Greimel et al., 2011; Kaufmann et al., 2010; but see Koschack, Kunert, Derichs, Weniger, & Irle, 2003) and adults (Müller et al., 2007) with ADHD. In addition, nonpsychotic relatives of individuals with schizophrenia have impaired divided attention (Faraone et al., 1999), as do adolescents scoring in the high-risk range on a questionnaire for psychotic-like experiences (Kim et al., 2012), suggesting it may be an endophenotype or risk factor. However, there has been no research that could shed light on the causal links between divided attention impairments and other forms of psychopathology.

Biased Attention

Biased attention is the tendency to direct attention toward, and have difficulty disengaging attention from particular type of affective stimuli, often those that are mood-congruent. Attentional biases can arise both from increased bottom-up salience of the affective stimuli (e.g., because it is mood-congruent) and reduced top-down control of attention. In the laboratory, attentional bias is usually measured in dot-probe tasks, in which visual attention must be directed away from affective stimuli to detect a target, and emotional Stroop tasks in which the meaning of affective words must be ignored to respond based on the color of the ink the words are written in (see Table 8.4).

The tendency to inappropriately allocate attention to emotional cues is central to cognitive models of mood disorders (e.g., Beck, 2008). Meta-analytic evidence demonstrates that individuals with depression have an attentional bias toward negative information, with medium effect sizes on dot-probe tasks, but only small effect sizes on emotional Stroop tasks (Table 8.4), and may have a bias away from positive stimuli (Peckham, McHugh, & Otto, 2010). Interestingly, attentional biases on the emotional Stroop and dot probe tasks do not appear to be significantly correlated, suggesting that they

TABLE 8.4 Examples of Commonly Used Attention Measures

Construct	Task	Description	Outcome measures	Methods citation[1]
Sustained attention	X-Type Continuous Performance Test	Stimuli (letters, numbers, or pictures) are presented continuously on the computer screen, participant presses a button whenever the target (e.g., X) appears.	Multiple measures including: **1.** Commission errors (false alarms) **2.** Omission errors **3.** RT **4.** Changes in RT and accuracy over time	Riccio, Reynolds, Lowe, and Moore (2002)
	AX-Type and Identical Pairs Continuous Performance Test	Stimuli (letters, numbers, or pictures) are presented continuously on the computer screen, participant presses a button whenever the target (e.g., X) appears, proceeded by a specific other stimulus (e.g., A), or when two identical stimuli appear in a row.	Multiple measures including: **1.** Commission errors (false alarms) **2.** Omission errors **3.** RT **4.** Changes in RT and accuracy over time	Riccio et al. (2002)
	Conners' Continuous Performance Test	Letters presented continuously on the computer screen, participant presses a button whenever any letter other than X appears.	Multiple measures including: **1.** Commission errors (false alarms) **2.** Omission errors **3.** RT **4.** Changes in RT and accuracy over time	Strauss et al. (2006)
	Integrated Visual and Auditory Continuous Performance Test (IVA)	Two stimuli (e.g., 1, 2) are presented pseudorandomly, alternating between visual and auditory presentation, participants press a button for targets, regardless of modality.	Standardized indexes calculated by the program, based on error and RT patterns	Strauss et al. (2006)
Selective attention	Ruff 2 & 7 Selective Attention Task	Draw lines through targets (2 & 7) while ignoring other numbers and letters.	**1.** Correct hits within time limit **2.** Errors	Strauss et al. (2006)
	Visual Search (e.g., Test of Everyday Attention search tasks)	Many versions. Search for target stimuli (e.g., a number, letter, shape, or picture) in an array of distracter stimuli.	Vary between versions, generally search time or number of correct hits within a time limit.	Strauss et al. (2006) for Test of Everyday Attention
	Dichotic Listening	Many versions. Two separate auditory stimulus streams (words or syllables) presented, one to each ear, via headphones. Participants asked to pay attention to one ear and repeat aloud the content.	**1.** Correct hits from attended ear **2.** Intrusions (false alarms) from unattended ear	Hugdahl (2003)
	Posner Cueing task and similar spatial cueing tasks	Participants must detect targets presented to the left or right of a fixation point, with or without a preceding cue. Cues are endogenous (central arrows pointing to the left or right) or exogenous (highlighting the left or right target box). On valid trials (usually 80%), the cue indicates the correct target location, on invalid trials (usually 20%), the cue indicates the incorrect target location.	Multiple measures including: **1.** Target detection RT **2.** Congruent RT—uncued RT (cueing benefit) **3.** Incongruent RT—uncued RT (incongruent cueing cost)	Posner, Snyder, and Davidson (1980)
Divided attention	Dual Task paradigms (e.g., Test of Everyday Attention Telephone Switch While Counting; Test of Attentional Performance divided attention task)	Many versions. Require completing two simple tasks at once, usually one visual and one auditory (e.g., visual search while counting tones in TEA). Performance compared with each task performed separately.	RT or accuracy difference between dual task and single task conditions	Strauss et al. (2006) for Test of Everyday Attention
Biased attention	Dot-Probe	Two stimuli (usually faces or other pictures) of differing valence are briefly presented (usually 500 ms) simultaneously on either side of a fixation point, followed by an emotionally neutral probe (e.g., dot, arrow, or letter) at one location, which must be detected/identified.	RT difference to detect/identify the probe in the previous location of the valences vs. the neutral stimulus	Yiend (2010)
	Emotional Stroop	Report the color of emotional words and neutral words written in colored ink.	RT difference between emotional and neutral words	Yiend (2010)

[1]Citations are for sources that provide a full description of the task and outcome measures of the most recent or recommended version of the task, not necessarily the first publication to report the task.

may index different attentional processes (Dalgleish et al., 2003). This could potentially be due to the need to shift visuospatial attention away from negative stimuli in the dot-probe tasks, in comparison to the emotional Stroop task, in which negative information is integral to the task stimuli. Depression is associated with extended maintenance of gaze to dysphoric stimuli in free viewing tasks, as measured with eye tracking (Armstrong & Olatunji, 2012), suggesting difficulty shifting visuospatial attention away from negative stimuli could potentially account for the stronger effects seen in dot-probe tasks. In contrast to depression, there is limited and mixed evidence for attentional biases toward negative and manic stimuli individuals with BD on emotional Stroop (Besnier et al., 2011; Lyon, Startup, & Bentall, 1999) and dot-probe (Lyon et al., 1999; but see Whitney et al., 2012) tasks. Thus, more research is needed on attentional biases associated with BD.

Attentional biases associated with depression and BD do not seem to be driven by current mood state, and may be risk markers. Negative attentional bias does not occur after sad mood induction (Epp, Dobson, Dozois, & Frewen, 2012) but is present in adults (Peckham et al., 2010) and youth (Hankin, Gibb et al., 2010) with depression in remission, and unaffected relatives of individuals with BD (Besnier et al., 2009; Gotlib, Traill, Montoya, Joormann, & Chang, 2004). Further supporting the hypothesis that attentional biases may be a risk factor, training to modify attentional biases by directing attention toward positive stimuli has been shown to reduce the risk of depression recurrence (Browning, Holmes, Charles, Cowen, & Harmer, 2012). However, one study did find that only depressed BD patients, and not euthymic BD patients or unaffected relatives of BD patients, demonstrated attentional bias away from positive stimuli (Jabben et al., 2012). Thus, more research is needed to determine if some attentional biases may be mood state dependent.

Like mood disorders, there is evidence for biased attention in anxiety disorders, specifically toward threatening stimuli. In emotional Stroop and dot-probe tasks, individuals with anxiety disorders have a bias toward threat information, with similar effect sizes across disorders, and for children and adults (Table 8.4). Likewise, individuals with PTSD have biased attention toward PTSD-specific threat words in the emotional Stroop task compared with nontrauma exposed individuals, though they do not differ significantly from trauma-exposed individuals without PTSD (Cisler et al., 2011). These attentional biases may be driven largely by initial orienting toward threat, as evidenced by larger effects at shorter stimulus durations (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van IJzendoorn, 2007) and more frequently initial orienting toward threat during free viewing and visual search (Armstrong & Olatunji, 2012). In contrast, there is not consistent evidence for increased subsequent maintenance of gaze toward threat, although it may occur in some task contexts (Armstrong & Olatunji, 2012). Thus, the factors that influence initial orienting of attention toward threat may be distinct from those that influence later maintenance or shifts of attention (Shechner et al., 2012).

Attentional biases have been relatively infrequently studied in individuals with schizophrenia, but the extant research suggests that schizophrenia may be associated with attentional biases toward disorder-specific stimuli. There is some evidence that individuals with paranoid schizophrenia have increased interference from paranoia-related and threat words in the emotional Stroop task (Besnier et al., 2011; Kinderman, Prince, Waller, & Peters, 2003), but not negative or positive words more generally (Besnier et al., 2011; Demily et al., 2010; Waters, Badcock, & Maybery, 2006). However, it is possible there is a more general bias toward negative stimuli in schizotypy (Mohanty et al., 2005). There has been almost no research on attentional biases in individuals with ADHD, with one recent study finding that children with ADHD did not exhibit the attentional bias toward threat shown by those with anxiety disorders (Weissman, Chu, Reddy, & Mohlman, 2012). More research is needed in this area, especially with stimuli that may be more affectively relevant to those with ADHD, such as reward stimuli.

Memory

Much of what we do in our daily lives, and indeed, who we are, depends on memory. There are multiple memory systems and memory processes, including *episodic memory* (memory for specific events), *semantic memory* (memory for facts and concepts), and *autobiographical memory* (memory for specific life events and facts about the self).[1] Memory problems are common in psychopathology, but the nature and magnitude of these impairments vary across disorders. While most forms of psychopathology are associated with impairments in episodic memory, only schizophrenia is associated with substantial impairments in semantic memory, and autobiographical memory

[1] Here we focus on explicit (episodic and semantic) memory, which has been most often studied in relation to psychopathology. Skill learning and conditioning can also be considered forms of memory (implicit memory), but are beyond the scope of this chapter. Working memory is covered in the section on executive function.

may be particularly affected in schizophrenia, depression and PTSD.

Episodic Memory

Episodic memory refers to memories for specific events within a spatio-temporal context (e.g., yesterday, I sat in my office and read papers about episodic memory), and relies heavily on the hippocampus and surrounding areas of the medial temporal lobe (e.g., Eichenbaum, 2004). In the laboratory, episodic memory is assessed by asking participants to study stimuli (e.g., word lists or complex designs), then recall or recognize them after a delay (Table 8.5). These tasks thus allow pure episodic memory to be separated from autobiographical memory for personally significant events. Many forms of psychopathology are associated with episodic memory impairments on these tasks, although the magnitude of these impairments varies both across disorders and across memory tests.

Adults with schizophrenia and bipolar disorders have similar profiles of episodic memory impairments, albeit with larger effect sizes for individuals with schizophrenia. Meta-analytic evidence demonstrates that individuals with schizophrenia and BD have large and medium impairments respectively in episodic memory (Table 8.6). Impairments are similar for recall of verbal and nonverbal information, and for recall after short and long delays (Table 8.6). There is some evidence that deficits in recognition are somewhat smaller than those for recall, although recognition memory has been less studied (Table 8.6). While there have been relatively few studies of episodic memory in children and adolescents with BD or early-onset schizophrenia, they seem to have somewhat comparable levels of impairment as adults with these disorders (Frangou, 2009; Joseph, Frazier, Youngstrom, & Soares, 2008). A recent meta-analysis also found that adolescents with psychosis risk syndrome have small but significant deficits in both verbal and nonverbal episodic memory, which are somewhat larger in those who go on to convert to schizophrenia (Giuliano et al., 2012).

There is some evidence that episodic memory impairments may be a stable trait in individuals with schizophrenia and BD. Deficits in individuals with BD are not closely tied to current mood state, as they occur in euthymic BD (Table 8.6), although there is some evidence that they may be somewhat larger in manic/mixed and depressed BD (Kurtz & Gerraty, 2009). In addition, in individuals with schizophrenia, meta-analyses of longitudinal studies have found no increase in deficits over relatively brief periods (Irani et al., 2011; Szöke et al., 2008). However, declines may occur over a longer time period, or may have already occurred since many studies included individuals with chronic schizophrenia.

There has been less research on episodic memory in other forms of psychopathology, but the available evidence points to episodic memory impairments in most other disorders as well. Adults with depression appear to have impairments in both verbal and nonverbal episodic memory (Table 8.6; but see Lee, Hermens, & Porter, 2012 for evidence of impaired nonverbal but not verbal episodic memory in first episode MDD). The one meta-analysis that included both recall and recognition measures for nonverbal memory found roughly equal effect sizes (Rock et al., 2013, Table 5). There has been no systematic examination as to whether verbal recall and recognition are differentially affected. In addition, there has been little research on episodic memory in children/adolescents with or at risk for depression, although a few studies have found deficits in verbal (Günther, Holtkamp, Jolles, Herpertz-Dahlmann, & Konrad, 2004; Horan, Pogge, Borgaro, Stokes, & Harvey, 1997) and nonverbal (Matthews & Coghill, 2008) episodic memory.

At least some anxiety disorders are also associated with episodic memory impairments. Individuals with PTSD have impairments in verbal episodic memory recall (after both short and long delays), but only small impairments in nonverbal recall (Brewin, Kleiner, Vasterling, & Field, 2007). An important question is whether these deficits are due to PTSD per se, or the traumatic experiences themselves. Both appear to contribute: individuals with PTSD have significant verbal episodic memory impairments even compared with trauma-exposed individuals without PTSD, but have larger impairments compared with healthy, nontrauma-exposed control participants (Table 8.6; Johnsen & Asbjørnsen, 2008). While most research included in these meta-analyses is on adults, studies in children with maltreatment-related PTSD have also reported episodic memory impairments (Carrion et al., 2012). However, there is some evidence that co-occurring depressive symptoms may account for episodic memory impairments in individuals with PTSD (Burriss, Ayers, Ginsberg, & Powell, 2008), and more research is needed to disentangle to what extent memory impairments are driven by factors specific to PTSD versus co-occurring depression or transdiagnostic processes.

Meta-analyses of adults with OCD found small but significant effect sizes for verbal memory and medium effect sizes for nonverb memory, but did not systematically analyze all specific aspects of memory (Table 8.6). A meta-analysis of compulsive checkers (most with a diagnosis of OCD) found significant, albeit moderate, impairments in verbal and nonverbal recall, and nonverbal

TABLE 8.5 Examples of Commonly Used Memory Measures

Construct	Task	Description	Outcome measures	Methods citation[1]
Verbal episodic memory	California Verbal Learning Test (CVLT)	Semantically structured list of 16 items presented for five learning trials, each followed by recall. Then a second 16 word interference list is presented for one trial, followed by free and cued recall of the first list. After 20 min. of distracting tasks, first list free and cued recall or repeated, then recognition test.	Many outcome parameters, including: **1.** Short delay free and cued recall **2.** Long delay free and cued recall **3.** Recognition (hits, false alarms, discrimination index)	Straus et al. (2006)
	Rey Auditory Verbal Memory Test (RAVLT)	List of 15 words read aloud by experimenter for five learning trials, each followed by recall. Then a second 15 word interference list is presented for one trial, followed by free recall of the first list. After a 20 min. delay, free recall of first list repeated, then recognition of first list words.	Many outcome parameters, including: **1.** Short delay free and cued recall. **2.** Long delay free and cued recall. **3.** Recognition (hits, false alarms, discrimination index).	Straus et al. (2006)
	Wechsler Memory Scale (WMS-III) Word List	Recall a list of 12 words after each of four learning trials, after presentation of an interference list, and again after a delay. Finally, a recognition trial is given.	**1.** Immediate recall **2.** Delayed recall **3.** Recognition	Straus et al. (2006)
	Wechsler Memory Scale (WMS-III) Logical Memory	Recall two paragraphs read aloud by the experimenter immediately and after a delay, followed by a yes/no recognition test.	**1.** Immediate recall **2.** Delayed recall **3.** Recognition	Straus et al. (2006)
	Wechsler Memory Scale (WMS-III) Verbal Paired Associates	Experimenter presents a list of word pairs, then reads the first word in each pair and participant must respond with the second word. Recall is re-tested after a delay, followed by a recognition test.	**1.** Immediate recall **2.** Delayed recall **3.** Recognition	Straus et al. (2006)
Nonverbal episodic memory	Benton Visual Retention Test (BVRT)	Geometric figure is displayed for 10 s and then withdrawn. Participant must copy figure from memory.	**1.** Number of correct reproductions **2.** Error score	Straus et al. (2006)
	Brief Visuospatial Memory Test (BVMT)	Participant views six simple geometric patterns in a grid for 10 s, which is then withdrawn. Participant must reproduce figures in correct locations from memory. Followed by two more learning and recall trials with same stimuli, then recall again after 25 min. of distracting tasks, followed by recognition trial.	Many outcome parameters, including: **1.** Recall on first three trials (short delay recall) **2.** Delayed recall **3.** Recognition (hits, false alarms, discrimination index)	Straus et al. (2006)
	Rey-Osterrieth Complex Figures Test (ROCF)	A complex geometric figure is presented. Administration procedures differ, but usually participants are asked to copy the figure, then it is withdrawn and participants must reproduce it from memory after a 3 min. delay and again after a 30 min. delay, which may be followed by a recognition trial.	Many outcome parameters, including: **1.** Short and long delay recall accuracy (points for each part of figure correctly reproduced). **2.** Recognition (points for each part of figure recognized correctly).	Straus et al. (2006)
	Wechsler Memory Scale (WMS-III) Visual Reproduction	Participant must reproduce geometric figures both immediately and after a delay. Recognition can also be tested.	**1.** Immediate recall **2.** Delayed recall **3.** Recognition	Straus et al. (2006)
	Wechsler Memory Scale (WMS-III) Faces	Participant must recognize faces both immediately after presentation and after a delay.	**1.** Immediate recognition **2.** Delayed recognition	Straus et al. (2006)
Semantic memory	Expressive Vocabulary Test (EVT), Boston Naming Test, and similar picture naming tests	Label pictures with increasing item difficulty. Some tests (e.g., EVT) also require providing synonyms for some items.	Scores based on number of items correct	Straus et al. (2006)
	Peabody Picture Vocabulary Test (PPVT) and similar picture recognition tests	Point to pictures corresponding to a label from an array of four pictures.	Scores based on number of items correct	Straus et al. (2006)

TABLE 8.5 (*Continued*)

Construct	Task	Description	Outcome measures	Methods citation[1]
	Wechsler Adult Intelligence Scale (WAIS) Vocabulary and similar vocabulary tests	Combination of naming pictures and defining words.	Standardized scores following scoring manual	Straus et al. (2006)
	Wechsler Adult Intelligence Scale (WAIS) Information and similar semantic information tests	Answering questions about a broad range of general knowledge, including scientific and geographical facts, history, and literature.	Standardized scores following scoring manual	Straus et al. (2006)
	Pyramid and Palm Trees/ Camel and Cactus	On each trial, point to one of four pictures that goes best with a target picture (e.g., target = bottle of wine, choices = apple, banana, grapes, pear).	Accuracy	Bozeat, Lambon Ralph, Patterson, Garrard, and Hodges (2000); Howard and Patterson (1992)
	Categorization/Sorting tasks	A variety of tasks, involving asking whether an item belongs to a certain category or not, or sorting items into categories, at different category levels (e.g., animals vs. plants; birds vs. mammals)	Accuracy	Doughty et al. (2009)
	Semantic Priming	A simple task, usually lexical decision (word or nonword) is performed, with each word proceeded by a semantically related word (prime) or unrelated word. Primes can be direct (e.g., tiger-lion) or indirect (e.g., stripes-lion).	Difference in RT between primed and unprimed words	Perea and Rosa (2002)
Autobiographical memory	Autobiographical Memory Interview	Semi-structured interview assessing semantic autobiographical memory (e.g., names of teachers) and episodic autobiographical memory (e.g., describing specific events) from childhood, early adulthood, and recent past.	**1.** Number of semantic facts recalled from each time period **2.** Points based on number and detail (time and place) of episodic events recalled from each time period	Straus et al. (2006)
	Autobiographical Memory Test	Participants are presented with words (e.g., safe, clumsy) and asked to retrieve a memory specific to time and place and describe it for 30–60 s.	Memories scored as categoric (repeated event), extended (lasting more than one day), or specific (reflect a unique occurrence lasting no longer than a day)	Williams and Broadbent (1986)
	TEMPau Task	Participants instructed to recall specific events (lasting less than one day) from different life periods, and classify them as remember (specific episodic details, sense of mental time travel), know (semantic details, sense of familiarity only), or guess (not certain about any details).	**1.** Overall and episodic specificity scores **2.** What, where, and when remember and know scores **3.** Self-perspective (field vs. observer)	Piolino, Desgranges, and Eustache (2009)

[1]Citations are for sources that provide a full description of the task and outcome measures of the most recent or recommended version of the task, not necessarily the first publication to report the task.

recognition, although verbal recognition was not impaired, possibly due to ceiling effects (Table 8.6; Woods, Vevea, Chambless, & Bayen, 2002). Research has focused almost entirely on adults, and the few studies in children and adolescents with OCD again show mixed findings of impaired (Andrés et al., 2007) and unimpaired (Ornstein, Arnold, Manassis, Mendlowitz, & Schachar, 2010; Shin et al., 2008) episodic memory. There has been very little research on memory function in individuals with other anxiety disorders. One study found significant verbal episodic memory impairments associated with PD and SAD, but not generalized anxiety disorder or specific phobias (Airaksinen et al., 2005; Galderisi et al., 2008). However, the lack of significant effects for specific phobias and generalized anxiety disorder must be interpreted with caution since the very small sample sizes limited power.

Finally, meta-analytic evidence demonstrates that adults with ADHD also have impairments in verbal episodic memory recall (after both short and long delays), and recognition (Table 8.6). While there has been no meta-analysis, individual studies have also found episodic verbal memory deficits in children and adolescents with

TABLE 8.6 Summary of Memory Meta-Analyses[1]

	Meta-analysis	Group	Short delay verbal recall	Long delay verbal recall	Verbal recognition	Short delay nonverbal recall	Long delay nonverbal recall	Nonverbal Recognition	Semantic memory
Depression	Lee et al. (2012)	First episode MDD	0.13			0.53		–	
	Rock et al. (2013)	MDD	–	–	–	0.50		–	0.44
	Zakzanis et al. (1998)[2]	MDD	0.79	0.95	–	0.86	0.65	–	–
	Herrmann, Goodwin, and Ebmeier (2007)	Early onset MDD	0.48 (episodic memory composite)						–
	Herrmann et al. (2007)	Late onset MDD	0.44 (episodic memory composite)						–
BD	Arts et al. (2008)	Euthymic BD (all)	0.82	0.85	–	–	–	–	–
	Bora et al. (2009)	Euthymic BD (all)	0.33	0.27	0.44	–	–	0.59	–
	Bora et al. (2011)	Euthymic BD II	–	–	0.22	–	–	–	–
	Kurtz and Gerraty (2009)	Euthymic BD (all)	0.74	0.80	–	0.78	–	0.86	–
	Kurtz and Gerraty (2009)	Manic/mixed BD (all)	–	1.05	–	–	–	–	–
	Mann Wrobel et al. (2011)	Euthymic BD (all)	0.67	0.80	0.42	0.67	–	–	0.09
	Robinson et al. (2006)	Euthymic BD (all)	0.73	0.71	–	–	–	–	–
	Stefanopoulou et al. (2009)	BD (all)	–	0.99	0.71	–	–	–	–
	Torres et al. (2007)	Euthymic BD (all)	0.74	0.72	–	0.43	–	–	0.08
Average			**0.67**	**0.77**	**0.45**	**0.63**	–	**0.73**	**0.09**
OCD	Woods et al. (2002)	Compulsive checkers	0.51		–0.17	0.66		0.49	–
	Abramovitch et al. (2013)	OCD	0.33 (verbal episodic memory composite)			0.76 (nonverbal episodic memory composite)			–
	Shin et al. (2013)	OCD	0.45		–	–	–	0.74	–
Average			**0.48**		**–0.17**	**0.66**	–	**0.70**	–
PTSD	Brewin et al. (2007)	PTSD	0.56	0.46		0.23	0.23		
Schizophrenia	Dickinson et al. (2007)	Schizophrenia	1.19	1.19	–	0.93	0.78	–	0.86
	Doughty and Done (2009)	Schizophrenia	–	–	–	–	–	–	0.78
	Forbes et al. (2009)	Schizophrenia	1.11	–	0.63	0.91	–	–	–
	Henry and Crawford (2005)	Schizophrenia	–	–	–	–			0.77
	Mesholam-Gately et al. (2009)	First-episode psychosis	1.20	0.90	0.57	0.95	0.90	–	0.84
	Pelletier et al. (2005)	Schizophrenia	–	–	0.71	–	–	1.00	–
	Stefanopoulou et al. (2009)	Schizophrenia	–	1.26	0.45	–	–	–	–
Average			**1.17**	**1.12**	**0.59**	**0.93**	**0.84**	**1.00**	**0.81**
ADHD	Frazier et al. (2004)	ADHD all ages	–	–	–	–	0.26	–	0.46
	Hervey et al. (2004)	ADHD adults	0.59	0.60	0.90	0.01	0.19	–	0.29
	Schoechlin and Engel (2005)	ADHD children and adolescents	–	–	–	–	–	–	0.27
Average (all ages)			**0.59**	**0.60**	**0.90**	**0.01**	**0.23**		**0.34**

[1] Summary of meta-analyses conducted in the last ten years. Weighted mean effect size (Cohen's *d*) comparing healthy control participants to the clinical group. All effect sizes have been recoded such that positive values represent worse task performance by the clinical group. When a meta-analysis reported effect sizes for multiple individual tasks within a memory component, the average of these effect sizes is reported.

[2] This older meta-analysis is included due to the lack of more recent meta-analyses covering multiple aspects of memory in individuals with MDD.

ADHD (Cutting, Koth, Mahone, & Denckla, 2003; Udal, Øygarden, Egeland, Malt, & Groholt, 2012; but see Kibby & Cohen, 2008; Vakil, Blachstein, Wertman-Elad, & Greenstein, 2012). However, there is little evidence of deficits in nonverbal episodic memory (Table 8.6). This pattern suggests that factors other than episodic memory per se may be contributing to the verbal memory deficits in individuals with ADHD. Since reading and language disorders frequently co-occur with ADHD (e.g., Willcutt, Pennington, & DeFries, 2000), it is possible that difficulty processing verbal information may play a role, although even children without co-occurring reading disabilities have been reported to have verbal episodic memory impairments (Cutting et al., 2003; Kibby & Cohen, 2008).

Overall, the pattern of episodic memory impairments across disorders suggests a domain-general deficit in encoding or retrieval. First, deficits are not greater for recall after a longer delay compared with a shorter delay in any disorder where this has been investigated. This suggests that psychopathology is associated with difficulty in encoding and/or retrieval, rather than forgetting more information over time (storage). Second, in most disorders, memory for both verbal and nonverbal materials is impaired, suggesting deficits are mostly domain general, although the magnitude of deficits occasionally differs between domains, perhaps due to additional domain-specific deficits (e.g., visuospatial processing in OCD (Rampacher et al., 2010). There are two possible exceptions, PTSD and ADHD, in which there is little evidence for nonverbal episodic memory impairments; however, as there has been less research on nonverbal memory in these disorders, it is premature to conclude that it is not impaired. Third, in some cases recall is more impaired than recognition. While recall requires retrieval processes supported by the hippocampus and PFC, recognition can be accomplished based on familiarity, which is supported by areas surrounding the hippocampus (Yonelinas, 2002).

Thus, it has been proposed that impaired hippocampal binding and prefrontally mediated use of strategies for encoding and retrieval lead to particular impairments in episodic recall for individuals with psychopathology (e.g., Barch & Ceaser, 2012). Indeed, there is meta-analytic evidence for reduced hippocampal volume and/or alterations in hippocampal functional activation in individuals with multiple forms of psychopathology, including schizophrenia (Adriano, Caltagirone, & Spalletta, 2012), BD (Frey et al., 2007), depression (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012), and PTSD (compared with both trauma-exposed and unexposed controls; Kühn & Gallinat, 2013; Woon, Sood, & Hedges, 2010; although effects have been much less consistently found in children; Carrion et al., 2012).

There is some evidence suggesting that hippocampally mediated memory problems may be risk factors or endophenotypes for psychopathology, rather than a neurodegenerative effect of illness. Hippocampal volume is reduced in at-risk individuals before psychosis onset (Fusar-Poli, Radua, McGuire, & Borgwardt, 2012), and is equally reduced in first episode and chronic schizophrenia (Adriano et al., 2012; Mesholam-Gately et al., 2009; Pelletier, Achim, Montoya, Lal, & Lepage, 2005) for increased recognition deficits with illness duration). Likewise, individuals who had lower episodic memory recall performance pre-trauma subsequently developed more PTSD symptoms following a natural disaster (Parslow & Jorm, 2007) or deployment to a war zone (Marx, Doron-Lamarca, Proctor, & Vasterling, 2009). Moreover, unaffected relatives of individuals with schizophrenia, BD, and PTSD also have smaller hippocampal volumes and moderate impairments in episodic memory (Arts et al., 2008; Barch, 2005; Bora et al., 2009; Gilbertson et al., 2006).

While this evidence suggests that hippocampal dysfunction may be an endophenotype, there is some evidence that neurodegenerative processes may also play a role. Specifically, stress has neurotoxic effects on the hippocampus, which has a particularly high concentration of glucocorticoid receptors (MacQueen & Frodl, 2010), suggesting that stress associated with psychopathology may contribute to hippocampal dysfunction. However, there is mixed and inconclusive evidence that hippocampal dysfunction increases with longer illness duration (MacQueen & Frodl, 2010), although there is evidence for progressive loss of temporal lobe grey matter (Vita, De Peri, Deste, & Sacchetti, 2012). Thus, hippocampal dysfunction may arise from a combination of neurodegenerative processes and genetic factors and early life stress which in turn increase risk for psychopathology (Pechtel & Pizzagalli, 2010).

Why might poor memory function serve as a risk factor? One possibility is that the ability to effectively solve problems depends in part on retrieval of information about similar past situations, and that poor problem solving increases stress and risk for psychopathology (e.g., Sutherland & Bryant, 2008). Moreover, under stress memories become more rigid and habitual, potentially contributing to a lack of flexibility in thinking and problem solving which could contribute to psychopathology (Schwabe, Wolf, & Oitzl, 2010).

Semantic Memory

Semantic memory is knowledge of facts and concepts, which are not tied to a particular time or place (e.g., knowing what semantic memory means, without remembering where and when you learned this). Semantic memory is generally assessed by asking people to define words, answer general factual questions, or sort items based on semantic categories or similarity (Table 8.5). Semantic memory depends on a distributed network of cortical areas that represent specific sensory properties (e.g., shapes and colors in visual association cortex, sounds in auditory association cortex) as well as anterior lateral temporal lobe and prefrontal areas involved in more abstract semantic processing (e.g., Patterson, Nestor, & Rogers, 2007).

Unique among the disorders reviewed here, meta-analytic evidence demonstrates that schizophrenia is associated with large impairments in semantic memory (Table 8.6). What is responsible for these semantic memory impairments? First, since many semantic memory tasks assess vocabulary and factual knowledge, performance could be affected by education; however, individuals with schizophrenia are impaired even compared with education-matched healthy control participants (Doughty & Done, 2009). Second, effect sizes are generally large for picture naming and vocabulary tests requiring language production, and moderate but still significant for picture matching and sorting tasks which do not require a verbal response (Doughty & Done, 2009). This suggests that language impairments may contribute to poor performance on verbal semantic memory tasks, but do not fully account for semantic memory impairments. Third, deficits are present even for naming and picture matching tasks that have few executive function demands and are generally preserved in individuals with prefrontal damage, suggesting that semantic memory deficits are also not solely due to EF impairments (Done, 2009).

Rather, schizophrenia may be associated with abnormalities in semantic associations themselves. Individuals with schizophrenia show bizarre associations, idiosyncratic categorization during sorting tasks, and increased semantic priming (especially indirect priming, e.g., tiger-stripe; Pomarol-Clotet, Oh, Laws, & McKenna, 2008), consistent with a loosening of associations caused by excessive spreading activation through semantic networks (Doughty & Done, 2009). These abnormalities in semantic associations are more severe for those with formal thought disorder, and have been posited to play a causal role in thought disorder (Pomarol-Clotet et al., 2008). However, while large deficits in semantic memory are already present in first episode psychosis (Mesholam-Gately et al., 2009), it is not known whether they precede illness onset.

In contrast to schizophrenia, semantic memory appears to only minimally impaired at most in individuals with other forms of psychopathology. Adults with BD show no deficit in vocabulary measures of semantic memory (Table 8.6). An older meta-analysis of adults with depression suggests only a small effect size on measures of semantic memory (Zakzanis, Leach, & Kaplan, 1998; Table 8.6), and a number of more recent studies have found no impairment on measures of semantic memory (Castaneda, Suvisaari, et al., 2008; Herrera-Guzmán et al., 2010; Matthews & Coghill, 2008b; but see Portella et al., 2003; Ravnkilde et al., 2002). ADHD is also associated with small deficits in semantic memory in both adults and children (Table 8.6), but as for verbal episodic memory, these deficits could potentially be driven by language difficulties, given that semantic memory is assessed with vocabulary and other verbal measures. There has been no meta-analysis of semantic memory in individuals with OCD, but individual studies suggest that performance on measures of vocabulary and semantic knowledge are not impaired (Andrés et al., 2007; Shin et al., 2008; Tekcan, Topçuoğlu, & Kaya, 2007; but see Exner, Martin, & Rief, 2009). There has been virtually no research on semantic memory in individuals with other anxiety disorders.

Autobiographical Memory

Autobiographical memory, which refers to memory about the self and one's own life, is considered to be a mixture of episodic memory for specific life events, and semantic memory for facts about the self (e.g., Renoult, Davidson, Palombo, Moscovitch, & Levine, 2012). Autobiographical memory is usually assessed using interview methods, in which people are asked to recall a serious of autobiographical events, and responses are scored for specificity (Table 8.5). In the Autobiographical Memory Test (AMT; Williams & Broadbent, 1986), participants are asked to retrieve a memory specific to a time and place in response to a serious of positive and negative cue words (e.g., safe, embarrassed), and responses are coded as specific (reflecting a specific event lasting no longer than a day), categorical (reflecting a repeated event), or extended (reflecting events extended over a long period of time). Autobiographical memory is considered *overgeneral* when most memories retrieved are categorical or extended rather than specific. Importantly, memories scored as specific in the AMT can contain both episodic and semantic details (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002).

In contrast, the Autobiographical Memory Interview (AMI; Kopelman, Wilson, & Baddeley, 1990) and Autobiographical Interview (Levine et al., 2002) provide indexes of both episodic and semantic autobiographical memory, by asking participants to recall specific life events and facts about the self, which are scored for the level of detail.

The main focus on autobiographical memory impairments has been on individuals with depression and PTSD. Overgeneral autobiographical memory in individuals with depression and PTSD is hypothesized to arise from (1) capture of attention by self-relevant information, activating ruminative processes that interfere with retrieval, (2) avoidance of retrieval of specific memories to regulate emotion, and (3) deficits in EF that limit the ability to successfully conduct retrieval searches of memory (for review, see Sumner, 2012). Meta-analytic evidence demonstrates that individuals with depression have large deficits in reporting specific autobiographical memories ($d = 1.12$; Williams et al., 2007). It is unclear if these deficits are specific to episodic versus semantic autobiographical memory, as most studies have used the AMT, but one recent study using the AMI reported impairment only on episodic autobiographical memory (Semkovska, Noone, Carton, & McLoughlin, 2012). Deficits in autobiographical memory associated with depression are not valence specific, as they have been reported for positive, negative, and neutral memory cues (see King et al., 2010 for review). In addition, autobiographical memory impairments persist during remission from depression, and thus are not dependent on current mood state (King et al., 2010).

Overgeneral autobiographical memory has been found in individuals with depression from childhood through older adulthood, although no systematic analysis of age-related changes has been conducted (King et al., 2010). The presence of autobiographical memory impairments early in life and depression course is consistent with additional evidence that autobiographical memory deficits may be associated with risk for depression. Overgeneral autobiographical memory predicts the onset of depression (but not anxiety or externalizing disorders) in adolescents (Hipwell, Sapotichne, Klostermann, Battista, & Keenan, 2011; Rawal & Rice, 2012), and future levels of depressive symptoms in adults even controlling for baseline symptoms (see Sumner, Griffith, & Mineka, 2010 for meta-analysis), although these predictive effects are small.

Despite detailed and intrusive memories of trauma events, there is also strong evidence for overgeneral autobiographical memory of nontrauma events in individuals with PTSD. PTSD and acute stress disorder are associated with reduced specificity of autobiographical memories, and this deficit cannot be accounted for by co-occurring depression or trauma exposure alone (see Brewin, 2011; Moore & Zoellner, 2007 for review). Indeed, the majority of the literature is not consistent with the view that trauma exposure alone (independent of PTSD symptoms) either in childhood or adulthood, leads to overgeneral autobiographical memory (Moore & Zoellner, 2007). Rather, there is some evidence that poor autobiographical memory may be associated with risk for developing PTSD: trainee firefighters who had more overgeneral autobiographical memory retrieval went on to develop more PTSD symptoms after three years of firefighting experience, during which they encountered multiple traumatic events (Bryant, Sutherland, & Guthrie, 2007). As in the depression literature, studies of autobiographical memory in individuals with PTSD have relied almost entirely on the AMT, which does not provide a separate measure of semantic autobiographical memory. However, there are reports that PTSD symptoms (Moradi et al., 2008), and traumatic experiences (Hunter & Andrews, 2002; Stokes, Dritschel, & Bekerian, 2008) are associated with worse semantic autobiographical memory.

Although autobiographical memory deficits associated with schizophrenia are less discussed, individual studies find evidence of impairment. Not surprisingly given impairments in both episodic and semantic memory, individuals with schizophrenia have difficulty recalling both autobiographical episodic and semantic memories, as indexed by both the number of memories recalled and their specificity and detail (e.g., McLeod, Wood, & Brewin, 2006; Neumann, Blairy, Lecompte, & Philippot, 2007). These deficits are not attributable to co-occurring depression or differences in premorbid IQ (McLeod et al., 2006). Autobiographical memories from all life stages, including early childhood, are affected, suggesting that the primary deficit arises during retrieval or that encoding is affected from early in development (McLeod et al., 2006). However, the largest impairment is for events and facts around the time of each individual's illness onset, suggesting that poor encoding during this time may contribute to autobiographical memory deficits (e.g., Riutort, Cuervo, Danion, Peretti, & Salamé, 2003). Interestingly, individuals with schizophrenia appear to also have difficulty generating detailed descriptions of possible future events (*prospective memory;* D'Argembeau, Raffard, & Van der Linden, 2008), which involves the same brain network activated by retrospective memory processes (e.g., Schacter, Addis, & Buckner, 2008).

There is very little research on autobiographical memory in individuals with other disorders. One study found overgeneral autobiographical memory in adults with BD (Scott, Stanton, Garland, & Ferrier, 2000). One study found that individuals with OCD had overgeneral autobiographical memory, but that this was driven by co-occurring depression rather than OCD per se (Wilhelm, McNally, Baer, & Florin, 1997). In general, autobiographical memory does not appear to be impaired in individuals with other anxiety disorders, including SAD (Heidenreich, Junghanns-Royack, & Stangier, 2010; Wenzel, Jackson, & Holt, 2002), or GAD/high worry (Finnbogadóttir & Berntsen, 2011; Wenzel & Jordan, 2005). Autobiographical memory has not been investigated in individuals with ADHD.

Thus, there is strong evidence for autobiographical memory impairments only in depression, PTSD, and schizophrenia. However, given the limited amount of research in individuals with other disorders, it is premature to draw conclusions about the specificity of autobiographical memory deficits to these disorders.

Gender, Cultural, and Ethnic Differences and Considerations

Basic cognitive processes are widely assumed to be human universals, and so not to vary greatly across cultures. Thus, while the aforementioned research included participants from many countries (including Asian, European, North American, and Latin American countries), there have been no systematic comparisons of cognitive process deficits across cultures. Socioeconomic status (SES) is perhaps a more likely moderator, as low SES is associated with worse performance on many cognitive tasks in both children and adults, with executive function perhaps most affected (see Hackman & Farah, 2009 for review). While many of these effects in adults are likely driven by education, which strongly influences performance on many tasks, SES effects are also found in infants and young children, thus education cannot be the only driving factor. Rather, there are multiple candidate causal pathways, including differences in parenting and chronic stress (Hackman & Farah, 2009). Since these factors are also known to affect risk for psychopathology, it seems plausible that SES could moderate the link between psychopathology and cognitive function. However, to our knowledge this has not been directly studied.

Gender has received somewhat more attention, given the differential rates of many forms of psychopathology between males and females. However, despite gender differences in psychopathology, there is not strong evidence that gender moderates the association between psychopathology and cognitive processes. Many meta-analyses have not examined gender as a potential moderator, and some that have done so have found that gender does not moderate cognitive impairments associated with psychopathology, including EF and attentional bias in depression (Peckham et al., 2010; Snyder, 2013), EF and episodic memory BD II disorder (Bora et al., 2011), and EF in ADHD (e.g., Lipszyc & Schachar, 2010; van Mourik et al., 2005). On the other hand, some meta-analyses have reported gender differences, including larger impairments in BD samples with more female participants on two measures of the shifting component of EF (Arts et al., 2008; Kurtz & Gerraty, 2009), but larger impairments for samples with more male participants in first-episode psychosis on measures of verbal episodic memory (Mesholam-Gately et al., 2009), and in ADHD for a measure of the inhibition component of EF (Bálint et al., 2009). However, these effects are generally found for one task, are not consistent across meta-analyses, and may not remain significant if other confounding moderators are controlled for (e.g., see (Lipszyc & Schachar, 2010) for an apparent effect of gender on inhibition in ADHD, which is no longer significant controlling for age and study quality). Thus, while gender effects merit further investigation, current evidence suggests that it is not a robust moderator of cognitive process deficits associated with psychopathology.

COGNITIVE PRODUCTS

Cognitive Styles

The following section outlines well-established maladaptive patterns of explaining stressful events or situations (Table 8.7). Some cognitive styles (e.g., negative inferential style, hostile attributional bias, looming maladaptive style) are event-specific, and although the style is consistent, the particular cognitions generated in response to each event are context dependent. Conversely, other cognitive styles (e.g., dysfunctional attitudes, early maladaptive schemas) are based upon stable mental representations, and are believed to be consistent across situations. Not only do these cognitive patterns involve assigning meaning to stressful situations in the environment, but they also involve the processing of self-related concepts.

Neuroimaging studies of cognitive styles have shown activation of the medial prefrontal cortex, which is associated with autobiographical content, as well as the anterior cingulate cortex, which is responsible for labeling incoming

TABLE 8.7 Commonly Used Cognitive Product Measures

Construct	Measure	Description	Methods citation
Attributional style: attributions for the cause of life events along three dimensions: **1.** internal vs. external **2.** stable vs. unstable **3.** global vs. specific	Attributional Style Questionnaire (ASQ)	Presents 12 hypothetical events (i.e., 6 are positive, 6 are negative; in addition, 6 are interpersonal, 6 are achievement related); participants indicate a cause of the event and answer questions about the cause of the event on a 7-point Likert scale	Peterson and Semmel (1982)
	Children's Attributional Style Questionnaire–Revised (CASQ-R)	Presents 24 hypothetical negative events; participants choose between two possible explanations for this event; each item holds two dimensions of attributional style constant, while the third is varied between the explanations	Thompson, Kaslow, Weiss, and Nolen-Hoeksema (1998)
Negative inferential style: attributions for the cause, consequences, and self-worth implications of life events along three dimensions	Cognitive Style Questionnaire (CSQ)	Presents 24 hypothetical events (i.e., 12 are positive, 12 are negative; in addition, 12 are interpersonal, 12 are achievement related). Participants indicate a cause of the event and answer questions about the cause, consequences, and self-worth implications of the event on a 7-point Likert scale	Haeffel et al. (2008)
	Adolescent Cognitive Style Questionnaire (ACSQ)	Presents 12 hypothetical negative events (i.e., 6 are interpersonal, 6 are achievement related). Participants indicate a cause of the event and answer questions about the cause, consequences, and self-worth implications of the event on a 7-point Likert scale	Hankin and Abramson (2002)
Dysfunctional attitudes: core beliefs about the world, relationships with others, and self that are related to performance, perfectionism, and approval by others	Dysfunctional Attitudes Scale (DAS)	Presents 40 dysfunctional attitude statements. Participants indicate agreement on a 7-point Likert scale (e.g., totally agree to totally disagree)	Weissman and Beck (1978)
	Children's Dysfunctional Attitudes Scale (CDAS)	Presents 40 dysfunctional attitude statements. Participants indicate agreement on a 4-point Likert scale (e.g., never true to always true)	Abela and Sullivan (2003)
Early maladaptive schemas: core beliefs about the world, relationships with others, and self that are related to childhood adverse relational experiences: **1.** disconnection: expectation that need for security, acceptance, and respect will not be met **2.** impaired autonomy: concerns about ability to function competently, capably, or independently **3.** other directedness: excessive focus on desires, feelings, and response of others **4.** overvigilance and inhibition: emphasis on suppressing feelings, impulses, and choices **5.** impaired limits: deficiency in internal limits, responsibility to others, and long-term goal orientation	Young Schema Questionnaire (YSQ)	Presents 205 schemas (75 schemas in the Short Form). Participants indicate agreement on a 6-point Likert scale (e.g., describes me perfectly to completely untrue of me)	Young and Brown (1994)
Looming maladaptive style: mental representation of future threat as rapidly rising in risk, progressively worsening, and accelerating.	Looming Maladaptive Style Questionnaire	Presents 6 hypothetical events. Participants answer questions about the event on a 5-point Likert scale	Riskind et al. (2000)
Hostile attribution bias: in ambiguous provocation situations, the tendency to interpret the intentions of another as hostile	Hypothetical situation instruments (multiple versions)	Presents hypothetical provocation situations (i.e., some are instrumental, some are relational) in which the intent is ambiguous; participants answer questions about the reasons for the provocation and intent of the provocateur	See, for example, Crick (1995) for questionnaire-based vignettes; Dodge, Pettit, McClaskey, and Brown (1986) for videotaped vignettes)

(*continued*)

TABLE 8.7 (*Continued*)

Construct	Measure	Description	Methods citation
Repetitive negative thought: self-focused attention that involves repetitively and passively focusing on negative events and symptoms of distress, as well as the causes and consequences of these events and symptoms	Response Style Questionnaire–Ruminative Responses Scale (RSQ–R)	Presents 22 statements regarding tendency to ruminate. Participants indicate agreement on a 4-point Likert scale (e.g., almost never to almost always)	Nolen-Hoeksema (1990)
	Children's Response Style Questionnaire (CRSQ)	Presents 10 statements regarding tendency to ruminate. Participants indicate agreement on a 5-point Likert scale (e.g., never to always)	Abela, Rochon, and Vanderbilt (2000)
	Penn State Worry Questionnaire (PSWQ)	Presents 16 statements regarding tendency to worry. Participants indicate agreement on a 5-point Likert scale	Meyer, Miller, Metzger, and Borkovec (1990)
Reappraisal: change how one thinks about a situation or about one's capacity to manage the demands of a situation to alter its emotional significance	Emotion Regulation Questionnaire (ERQ)	Presents 10 items that assess trait use of reappraisal and suppression. Participants indicate agreement on a 7-point Likert scale	Gross and John (2003)
Distraction: engaging in thoughts or behaviors to divert one's attention away from negative mood and instead toward more positive stimuli	Response Style Questionnaire–Distractive Responses Scale (RSQ–D)	Presents 11 statements regarding tendency to distract; participants indicate agreement on a 4-point Likert scale (e.g., almost never to almost always)	Nolen-Hoeksema (1990)
	Children's Response Style Scale (CRSQ)	Presents 10 statements regarding tendency to distract. Participants indicate agreement on a 5-point Likert scale (e.g., never to always)	Abela, Rochon, and Vanderbilt (2000)

information as self-referential (for a review, see Disner, Beevers, Haigh, & Beck, 2011). Furthermore, these studies have found increased activation of the amygdala and hippocampus–limbic structures involved in emotional processing (see Disner et al., 2011). These particular regions exhibit increased activity among participants with psychopathology, such as depression (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010) and social anxiety (Blair et al., 2008). Therefore, neuroimaging studies suggest that maladaptive patterns of self-referential processing in the context of stressful life events may be associated with emotional distress, and consequently, psychopathology.

Negative Inferential Style

Broadly defined, negative inferential style refers to an individual's characteristic pattern of explaining the meaning, causes, and consequences of stressful life events. One particular type of negative inferential style was outlined originally in the reformulated learned helplessness theory of depression (Abramson et al., 1978), which maintains that individuals who attribute negative events to internal (i.e., about the self), stable (i.e., enduring), and global (i.e., widespread) causes are said to possess a negative attributional style. An extension of the reformulated learned helplessness theory is the hopelessness theory of depression (Abramson, Metalsky, & Alloy, 1989). According to this model, individuals not only possess a negative attributional style for the *causes* of stressful life events, but they also make stable and global inferences regarding the *consequences* of an event and believe that a stressful life event has negative implications for the *self* (e.g., the self is deficit, flawed, or worthless).

Empirical research examining the role of negative inferential style as a cognitive vulnerability to psychopathology has found support in children, adolescents, and adults, although relatively less research with child samples suggests that more research needs to be conducted in this early cohort to fully understand the nature of the relationship between negative inferential style and psychopathology. More importantly, a substantial body of research has found that negative inferential style interacts with negative life events to predict changes in psychopathology, including symptoms and clinical diagnosis, over time. Although originally formulated as a theory to explain vulnerability to depression, it appears as though a negative attributional style is present across other types of psychopathology, such as PTSD, ADHD, and schizophrenia.

Findings linking negative inferential style to depression, in particular, are the most robust compared with other forms of psychopathology. Numerous cross sectional studies have demonstrated a relationship between negative inferential style and depression in children, adolescents, and adults (Alloy et al., 2012; Alloy, Abramson, Walshaw, & Neeren, 2006). Although informative, cross sectional methodology makes it difficult to determine whether negative inferential style reflects a risk factor, causal risk factor, correlate, or consequence of depression. Studies that utilize more than one time point are best able to

examine whether negative inferential style precedes and prospectively predicts changes in depression over time. Such studies have found that negative inferential style predicts changes in depression in children, adolescents, and adults (e.g., Abela & Hankin, 2008; Abramson et al., 2002; Alloy, Abramson, Walshaw, & Neeren, 2006). More specifically, negative inferential style prospectively predicts levels of depressive symptoms, first onsets of depression, as well as recurrence of depression in adults (e.g., Alloy et al., 2000), which is consistent with the risk factor model. Additionally, studies with remitted depressives can also be helpful in determining whether negative inferential style is mood-state dependent, or whether it represents a stable and enduring trait. Unfortunately, studies that have examined remitted depressives have produced mixed results. A majority of studies have found that remitted depressives do not exhibit negative inferential style, whereas a few studies have shown that these individuals do in fact demonstrate this type of cognitive vulnerability after recovering from depression (see Alloy et al., 2006). Therefore, there is insufficient evidence to conclude whether negative inferential styles represent a consequence of depression.

It is also important to examine the role of stressful life events as a moderator of the relationship between negative inferential style and depression. It should be emphasized that in the cognitive vulnerability–stress model, negative inferential styles contribute to psychopathology only in the presence, not the absence, of stressful life events. Studies that examine the interaction of negative inferential style and stressful life events therefore provide a more stringent test of these models. Such studies have found consistent support for the vulnerability–stress model in predicting changes in depressive symptoms as well as the occurrence of a clinically significant depressive episode in both children and adolescents (e.g., Abela & Hankin, 2008; Jacobs, Reinecke, Gollan, & Kane, 2008; Lakdawalla, Hankin, & Mermelstein, 2007) and adults (e.g., Abramson & Alloy, 2006; Abramson et al., 2002; Ingram, Miranda, & Segal, 2006; Joormann, 2010).

A subset of research on negative cognitive style and depression has separately examined the specific role that each type of inference (e.g., cause, consequence, implication for the self) plays in the development of depression. Studies that have parsed out negative inferential style into three factors have yielded mixed findings. Some studies have found support for all three types of negative inferences as a predictor of increases in depressive symptoms when combined with hassles (e.g., Brozina & Abela, 2006). In some youth samples, researchers have found that negative inferences about the *self*, but not about the causes or consequences regarding negative events, interacted with stress to predict changes in depressive symptoms over time (Abela, McGirr, & Skitch, 2007; Cohen, Young, & Abela, 2011). However, other studies with youth have found that only inferences about the *causes* of negative events interact with stress to predict changes in depression (e.g., Conley, Haines, Hilt, & Metalsky, 2001; Lau, Rijsdijk, Gregory, McGuffin, & Eley, 2007). Still others have demonstrated that negative inferences about the *consequences* of negative events predict changes in depression (Abela, 2001; Cohen, Young, & Abela, 2011). It has been suggested that one specific type of inference may not be the strongest predictor of depression for all individuals, especially children and early adolescents. Rather, each individual is as vulnerable to depression as his or her most negative inferential style, a theory known as the *weakest link approach* (Abela & Sarin, 2002). The weakest link approach should inform studies that choose to parse out negative inferential style, such that these studies should determine a participant's most negative inference as reflective of that participant's overall cognitive vulnerability. Studies using this approach to study the cognitive vulnerability–stress model have found support (Abela & Hankin, 2008).

The relationship between negative inferential style and BD is similar to that of depression. Cross sectional studies with bipolar individuals currently experiencing a depressive episode found that negative inferential styles did not differ from those of unipolar individuals who were also currently depressed (Reilly-Harrington & Alloy, 1999; Reilly-Harrington & Miklowitz, 2010). As with studies of remitted individuals with depression, studies with remitted individuals with BD have been mixed. A majority of studies report that remitted individuals do not exhibit more negative inferential styles than healthy individuals, whereas other studies do find a significant difference between these two groups (Alloy, Abramson, Walshaw, Keyser, & Gerstein, 2006; Lex, Hautzinger, & Meyer, 2011). In a similar vein, some studies have found that negative cognitive style remained stable across different mood states in bipolar individuals, including hypomania, depression, and euthymia (Reilly-Harrington & Miklowitz, 2010). Cross sectional studies with bipolar individuals in hypomanic and manic states also found evidence for negative inferential styles (Lex et al., 2011; Reilly-Harrington & Alloy, 1999; Reilly-Harrington & Miklowitz, 2010; Scott & Pope, 2003), but these were only found in those who had a past history of depression. Those without depression did not differ from healthy controls. Longitudinal studies have found that negative cognitive styles interact with stressful life events to predict changes in

depressive symptoms, as well as manic symptoms, in individuals diagnosed with BD (Reilly-Harrington & Alloy, 1999) as well as individuals with subsyndromal levels of bipolar symptoms (Reilly-Harrington & Alloy, 1999).

Research with bipolar individuals has also found a link between positive inferential style and mania. Individuals with a positive inferential style make stable and global attributions for the causes of positive events, anticipate positive consequences as a result of these positive events, and identify positive implications for the self as a result of these events (Alloy, Abramson, Walshaw, & Neeren, 2006). Cross sectional findings show that bipolar individuals in a manic state exhibit a positive inferential style (Lex et al., 2011), which when combined with positive life events, prospectively predicts increases in hypomanic symptoms (Alloy, Abramson, Walshaw, Keyser, et al., 2006). Taken together, findings for both negative and positive inferential style in BD are consistent with the risk factor model.

Most studies with both youth and adults have shown that a negative inferential style is not associated with certain forms of anxiety symptoms or anxiety disorder either as a main effect predictor or in the context of stressful life events (e.g., Alloy, Abramson, Whitehouse, Hogan, et al., 2006; Hankin, Abramson, Miller, & Haeffel, 2004; Hankin, 2008; Joiner, 2000). However, a recent study by Alloy et al. (2012) found that negative inferential styles were concurrently associated with anxiety symptoms and diagnoses (e.g., social phobia). This discrepancy may be due to the fact that the sample in Alloy et al. (2012) was largely composed of early adolescents, which is a critical developmental period for first onset of anxiety disorders. Depression, on the other hand, typically emerges in mid- to late adolescence or early adulthood. In addition, many studies linking negative inferential style and depression found that negative inferential style was higher among individuals diagnosed with *comorbid* anxiety and depression compared with those diagnosed with only depression or only anxiety (Alloy, Abramson, Whitehouse, Hogan, et al., 2006; Fresco, Alloy, & Reilly–Harrington, 2006). Prospective longitudinal studies have demonstrated that individuals with high levels of negative attributional style were more likely to experience an onset of an anxiety disorder that was comorbid with depression compared with low-risk individuals (Alloy, Abramson, Walshaw, & Neeren, 2006).

Despite the lack of support for negative inferential style as a cognitive vulnerability for anxiety broadly defined, a small line of research has found associations between attributional style and PTSD, specifically (Elwood, Hahn, Olatunji, & Williams, 2009). Individuals who attribute interpersonal and noninterpersonal traumatic events to stable and global causes experience more severe PTSD as well as prospective increases in PTSD symptoms over time (Elwood, Hahn, et al., 2009; Palker-Corell & Marcus, 2004; Runyon & Kenny, 2002; Williams, Evans, Needham, & Wilson, 2002). In addition, some other studies have reported that individuals who attribute these events to external causes also report higher levels of PTSD (Elwood, Hahn, et al., 2009). In sum, there is little support for the role of negative inferential styles in anxiety generally, however, a line of research examining PTSD in particular has found support for an external, stable, and global style among individuals with PTSD.

There is a small body of research linking negative inferential style and ADHD (see Rucklidge, Brown, Crawford, & Kaplan, 2007 for a review). It is hypothesized that individuals with ADHD most likely experienced a higher rate of repeated experiences of failure, and if undiagnosed, teachers and parents might have attributed these difficulties to characteristics of the individual (e.g., lazy, stupid, unmotivated). As in depression, individuals with ADHD tend to make stable and global attributions for negative events as well as unstable and specific attributions for positive events (Collett & Gimpel, 2004; Rucklidge & Kaplan, 2000). In addition, another type of negative inferential style that is most commonly associated with ADHD involves a hypothesized fourth dimension, known as controllability (see Rucklidge & Kaplan, 2000 for a discussion). This dimension reflects the degree to which the causes and consequences of negative events are viewed by individuals as within their control. Researchers have found that individuals with ADHD possess an internal-uncontrollable inferential style, such that they believe that their cognitive and behavior problems are the result of variables that are internal, but also out of their control (Rucklidge et al., 2007). In line with this theory, studies have found that adults with ADHD tended to make internal and uncontrollable attributions for negative events in their childhood (Rucklidge et al., 2007) as well as for current negative events (Rucklidge & Kaplan, 2000). This pattern is also found in children and adolescents with ADHD (Rucklidge et al., 2007; Rucklidge & Kaplan, 2000). Very few studies have examined associations between negative attributional style and conduct disorder/oppositional defiant disorder (CD/ODD). These studies have found that the interaction of attributional style and stressful life events has exhibited specificity with depression, and did not predict externalizing symptoms over time (Hankin, 2008b; Robinson, Garber, & Hilsman, 1995).

Studies of negative inferential style in schizophrenia have mostly examined the internal/external domain

for attributions regarding the causes of negative events. Healthy individuals typically attribute negative events to external causes, but these causes are more likely to be universal (i.e., due to chance or circumstance), as opposed to personal (i.e., due to other individuals; Aakre, Seghers, St-Hilaire, & Docherty, 2009). Individuals with schizophrenia, especially those currently experiencing persecutory delusions, tend to attribute negative events to external personal causes (Aakre et al., 2009). Individuals with schizophrenia who are not currently paranoid, however, do not attribute negative events to external-personal causes (Aakre et al., 2009). Therefore, the attributional style of individuals with schizophrenia appears to be a state dependent correlate of schizophrenia, and not a stable and enduring cognitive pattern.

Dysfuncational Attitudes

Beck's cognitive theory of psychopathology posits that self-schemas are associated with the onset, maintenance, and recurrence of emotional disorders, such as depression (Beck, 1976). Broadly speaking, schemas are well-organized cognitive representations of the past experiences that represent an individual's knowledge of the world, relationships with others, and the self. Depressive self-schemas, in particular, represent a set of rigid core beliefs or dysfunctional attitudes related to performance, perfectionism, and self-worth, and guide the selective processing of negative information in the environment over and above positive or neutral information (Dozois & Beck, 2008). In the presence of stressful life events, these depressive self-schemata act as filters for stimuli in the environment, affecting the way an individual perceives, encodes, interprets, and remembers emotionally salient information (Beck, 1976; Dozois & Beck, 2008; Joormann & Gotlib, 2010). This selective processing of negative information contributes to negative automatic thoughts, and consequently, negative perception about oneself, the world, and the future—the negative cognitive triad (Dozois & Beck, 2008). This negatively biased information processing ultimately leads to the onset of emotional distress symptoms or disorders. Although there is conceptual and empirical overlap between dysfunctional attitudes and negative inferential style, dysfunctional attitudes represent universal beliefs and rules, as opposed to event-specific attributions inherent in negative inferential style. Indeed, studies have shown that measures of dysfunctional attitudes and negative inferential style load onto distinct latent factors (e.g., Haeffel et al., 2003; see Taxonomy and Structure of Cognitive Risks section in Discussion).

In addition to an overall cognitive vulnerability–stress model for dysfunctional attitudes, Beck (1987) has hypothesized that the experience of stressful events that are congruent with one's own particular cognitive schema should confer particular vulnerability to the development of depression (Zuroff, Mongrain, & Santor, 2004). These particular schemas are divided into two categories: sociotropy and autonomy. Individuals with a sociotropic cognitive style value intimacy, relationships, and acceptance from others, and consequently, are most vulnerable to emotional distress when they experience rejection, loss, and disappointment in the interpersonal domain (Beck, 1987). Those with an autonomic cognitive style place great importance on achievement, independence, and control, and so are at a greater risk for distress when they experience failure or are precluded from making their own choices (Beck, 1987).

Young, Klosko, and Weishaar (2003) extended the work of Beck and identified a variety of early maladaptive schemas (EMS) that underlie several forms of psychopathology. These maladaptive schemas are pervasive patterns of memories, emotions, cognitions, and bodily sensations that represent an individual's knowledge about the world, relationships with others, and the self. These schemas guide the appraisal of situations, such that the individual focuses on elements that confirm the schema and minimize or deny information that contradicts the schema, thus perpetuating the schema. Young's early maladaptive schemas fall into five domains: *disconnection/rejection*, *impaired autonomy*, *other-directedness*, *impaired limits*, *overvigilance/inhibition*. Individuals who are high on the disconnection/rejection domain believe that others will not meet their needs for security, acceptance, and respect. Such individuals fear being rejected by others and anticipate that certain negative events will lead to negative evaluation and loss of status. Those who are high on the impaired autonomy domain anticipate that aspects of the self and the environment will interfere with their ability to function independently and successfully. Other-directedness is related to an extreme focus on the desires of others, even at the expense of the individual's needs. Impaired limits encompasses characteristics such as difficulties exerting self-control. Finally, overvigilance and inhibition includes particular schemas, such as negativity/pessimism, emotional inhibition, and punitiveness.

Overall, dysfunctional attitudes and early maladaptive schemas have shown a robust relationship with depression, anxiety, BD, and schizophrenia, with fewer studies examining the relationship with externalizing disorders. As with negative inferential style, both dysfunctional attitudes and

early maladaptive schemas are linked to psychopathology as main effect predictors, as well as in the context of negative life events. Dysfunctional attitudes demonstrate the strongest associations with depression in children, adolescents, and adults both concurrently and prospectively over time (Abela & Hankin, 2008; Abramson et al., 2002; Alloy, Abramson, Walshaw, & Neeren, 2006; Jacobs et al., 2008). In addition, the interaction of dysfunctional attitudes and negative life events is linked to increases in depressive symptoms in adults (Abramson et al., 2002; Joormann, 2010) as well as adolescents (Abela et al., 2011; Hankin et al., 2009). Similar findings have been demonstrated for clinically significant depressive episodes with adolescents (Lewinsohn, Joiner, & Rohde, 2001) and adults (Hankin et al., 2004; Otto et al., 2007). This constitutes solid evidence for dysfunctional attitudes as a risk factor for the development of depression.

Studies of early maladaptive schemas in nonclinical adult samples have found that specific schemas falling under the domains of disconnection and rejection, impaired autonomy and other-directedness interacted with stressful life events to predict increases in depressive symptoms over time (Cámara & Calvete, 2011; Eberhart, Auerbach, Bigda-Peyton, & Abela, 2011). Cross sectional studies (Lumley & Harkness, 2007; Muris, 2006; Vlierberghe, Braet, Bosmans, Rosseel, & Bögels, 2009) and one longitudinal study (Calvete, Orue, & Hankin, 2012) of adolescents have found that these three domains are associated with depression in adolescents.

Dysfunctional attitudes have been shown to relate specifically to depression, and not anxiety generally, both concurrently and prospectively (e.g., Alloy, Abramson, Walshaw, & Neeren, 2006; Hankin, Abramson, Miller, & Haeffel, 2004). However, studies of early maladaptive schemas, in particular, have found that the domain of impaired autonomy, which includes vulnerability to harm and dependence, predicted increase in anxiety symptoms in the context of stressful life events (Cámara & Calvete, 2011; Glaser, Campbell, Calhoun, Bates, & Petrocelli, 2002; Lumley & Harkness, 2007; Schmidt, Joiner, Young, & Telch, 1995; Welburn, Coristine, Dagg, Pontefract, & Jordan, 2002). In terms of SAD, specifically, one study has identified the other-directedness schema domain as a significant predictor of social anxiety symptoms over time (Calvete, Orue, & Hankin, 2012). Studies in the PTSD literature have identified mistrust/abuse, defectiveness/shame, emotional deprivation, dependency, and vulnerability to harm as particularly related to early traumatic and victimization experiences (Harding, Burns, & Jackson, 2011; Price & Mohlman, 2007b).

Few studies have explored the relationship between early maladaptive schemas and BD. Nilsson, Jørgensen, Straarup, and Licht (2010) found that individuals diagnosed with BD were higher on the domain of impaired limits, especially insufficient self-control, compared with healthy controls. Hawke, Provencher, and Arntz (2011) also found that impaired limits, specifically entitlement/grandiosity and insufficient self-control/self-discipline, was associated with BD. The authors also identified a negative relationship between emotional inhibition and BD.

Although early maladaptive schemas have not been studied in individuals with externalizing disorders, a smaller number of studies have examined the link between early maladaptive schemas and aggression. Calvete (2008) found that entitlement/grandiosity was the strongest predictor of aggressive behavior. Similarly, Rijkeboer and De Boo (2010) identified defectiveness/shame, mistrust/abuse, entitlement/grandiosity, and insufficient self-control schemas in relation to aggressive mood in children.

Finally, a small body of research in dysfunctional attitudes in schizophrenia has found that these individuals demonstrate a great deal of concern with their performance and other's evaluation of their performance (Rector, 2004). Patients with schizophrenia possess maladaptive beliefs about their ability to succeed in various activities, and as a result, have low levels of interest and motivation in engaging in these activities (i.e., negative symptoms; Rector, 2004). In addition, individuals with schizophrenia also are concerned about how they are perceived by others (Grant & Beck, 2009; Horan et al., 2010; Rector, 2004).

Hostile Attribution Bias

Hostile attribution bias is a type of attributional style that is based upon social information processing theory (Crick & Dodge, 1994). Broadly speaking, social information processing involves five stages: encoding of social cues, interpretation of cues, response access, response evaluation, and response enactment (Mathieson, Murray-Close, Crick, & Woods, 2011). Hostile attribution bias is grounded in the second stage of processing: interpretation of cues. In this stage, an individual assigns meaning to social cues that have been perceived, attended to, and stored in short-term memory during the encoding stage. The interpretation of social cues is contingent upon two factors: the nature of encoded social cues (e.g., quantity, sensory modality, emotional valence), as well as the ability of the individual to utilize those social cues to infer others' intentions and beliefs. In hostile attribution bias, individuals interpret the intentions of others as hostile in ambiguous social situations (Andrade et al., 2012; Crick & Dodge, 1994; Dodge,

1980; Mathieson & Murray-Close, 2011; Orobio de Castro, Veerman, Koops, Bosch, & Monshouwer, 2002). Therefore, a hostile attribution bias is the result of a maladaptive pattern of inferring others' intentions and beliefs.

A preponderance of evidence has demonstrated an association between hostile attribution bias and subsequent aggressive behavior. In addition, there is evidence that individuals with schizophrenia, especially those with paranoia or persecutory delusions, may exhibit hostile attribution bias. Finally, very few studies have found evidence of hostile attributional style among children who are high in depression and anxiety. To our knowledge, there are no studies of hostile attribution bias in BD.

The link between hostile attribution bias and aggressive behavior is robust and has been found among community populations of elementary and junior high school age youth (Andrade et al., 2012; Crick, Grotpeter, & Bigbee, 2002), clinical populations of youth (MacBrayer, Milich, & Hundley, 2003), incarcerated offenders (Dodge, Price, Bachorowski, & Newman, 1990), and adults (DeWall, Twenge, Gitter, & Baumeister, 2009; Dodge, 2006). Prospective longitudinal studies have also found that hostile attribution bias predicts changes in aggression over time (Dodge, 2006), which suggests that this type of bias may serve as a risk factor. Some studies that examine the link between social rejection and subsequent aggression have found that hostile attribution bias mediates this link (DeWall et al., 2009; Reijntjes et al., 2011; Yeung & Leadbeater, 2007).

There is some discussion in the hostile attribution literature of specificity between the type of provocation situation, the hostile attribution bias, and the type of retaliatory aggression. Aggressive behavior is typically classified along two specific dimensions (Crick & Grotpeter, 1995). Physical aggression involves the use or threat of physical force to influence perceptions of safety and power. Relational aggression, on the other hand, involves damage to relationships through mechanisms such as friendship withdrawal, manipulation of social status among peers, or gossiping. Researchers have found some support for this hypothesized specificity. For instance, individuals who were relationally aggressive exhibited hostile attribution biases for ambiguous provocation scenarios that were relational in nature (Bailey & Ostrov, 2007; Crick & Grotpeter, 1995; Crick et al., 2002; Yeung & Leadbeater, 2007). In addition, physically aggressive individuals demonstrated hostile attribution biases for ambiguous provocation scenarios that were instrumental or physical in nature (Bailey & Ostrov, 2007; Crain, Finch, & Foster, 2005; Crick et al., 2002). However, other researchers have not found these exact relationships. For instance, Godleski & Ostrov (2010) found that hostile attributions for instrumental provocations predicted both physical and relational aggression.

In light of evidence that children with ADHD are also particularly prone to act aggressively in social situations, a small body of literature has also explored hostile attribution bias in individuals with this disorder. Attentional difficulties in ADHD cause individuals to encode fewer social cues in experimental vignettes, and as a consequence these children do not have the same amount of relevant social cue information with which to make response decisions (Andrade et al., 2012). In negatively valenced vignettes, children with ADHD make significantly more negative intent attributions than controls (Andrade et al., 2012).

In addition to disorders characterized by externalizing behaviors, some research has explored hostile attribution bias in schizophrenia. Findings show that individuals with paranoia or persecutory delusions make hostile attributions by consistently blaming other people for negative events (e.g., personalizing bias, Penn, Sanna, & Roberts, 2008). Finally, a few studies have examined the role of hostile attributional style in depression and anxiety. Quiggle, Garber, Panak, and Dodge (1992) found that children with high levels of depressive symptoms showed a hostile attributional bias. Bell-Dolan (1995) found that anxious children identified hostile intent within nonhostile vignettes, whereas the control children did not. Because these were cross sectional studies, no conclusions can yet be made as to whether hostile attribution bias may also serve as a risk factor for these disorders.

Looming Maladaptive Style

The looming maladaptive style (Riskind, Williams, Gessner, Chrosniak, & Cortina, 2000) is based on a danger or threat schema and is traditionally associated with anxiety, and not depression. These danger or threat schemas are hypothesized to lead to the formulation of biased expectations about the temporal and spatial progression of potential threats, such that these threats are perceived as rapidly mounting, escalating, or approaching the individual (Riskind et al., 2000). As a result of this active and dynamic perception of threat, individuals interpret even mundane situations as being potentially dangerous, and therefore initiate cognitive processes to assess these situations.

Findings have shown that looming maladaptive style is concurrently associated with both clinical and subclinical anxiety disorders (Riskind et al., 2000). In addition,

looming maladaptive style is a prospective predictor of changes in anxiety symptoms overall (Williams, Shahar, Riskind, & Joiner, 2005) as well as changes in specific types of anxiety symptoms, such as OCD (Elwood, Riskind, & Olatunji, 2009; Riskind, Tzur, Williams, Mann, & Shahar, 2007), SAD (Brown & Stopa, 2008), generalized anxiety (Williams et al., 2005) and PTSD (Elwood, Williams, Olatunji, & Lohr, 2007).

Because looming maladaptive style is conceptualized to relate specifically to anxiety, no study has examined its role in other internalizing disorders (e.g., depression and BD), externalizing disorders (e.g., ADHD, aggression), or schizophrenia. However, the fact that looming maladaptive style is a way of identifying, interpreting, and categorizing information that is grounded in schemas suggests some conceptual relation to previously discussed schema theories (Beck, 1967;Young et al., 2003).

Repetitive Negative Thought

This section describes various forms of repetitive negative thought. The response style theory (Nolen-Hoeksema, 1991) defines repetitive negative thought, or rumination, as a type of self-focused attention that involves repetitively and passively focusing on negative events and symptoms of distress, as well as the causes and consequences of these events and symptoms (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). It is important to note that the defining feature of rumination is the *process* of perseverative thinking, and not necessarily the *content* of the thinking. More recently, theorists have determined two distinct components within the greater construct of rumination (Treynor, Gonzalez, & Nolen-Hoeksema, 2003). The first component, called *brooding*, involves negative and self-critical thinking about the self (Watkins, 2008). Brooding is considered to be a maladaptive component of rumination and is positively associated with negative mood (Rood, Roelofs, Bögels, Nolen-Hoeksema, & Schouten, 2009). *Reflective pondering*, on the other hand, represents contemplation of symptoms of distress and negative events to better engage in problem solving behaviors (Watkins, 2008). This is the adaptive component of rumination and is negatively associated with negative mood (Roelofs et al., 2009).

Rumination is associated with various forms of psychopathology, especially depression, anxiety, and aggression. There is a lack of studies that have explored rumination among individuals with ADHD and schizophrenia, however. It is important to note that the process of rumination is nearly identical across these disorders, however the *content* of ruminative thought demonstrates content-specificity (e.g., sadness in depression, anger in aggression). Similar to cognitive styles, repetitive negative thought activates regions of the brain associated with self-referential processing, such as the medial prefrontal cortex, anterior cingulate cortex, and amygdala. For instance, the medial prefrontal cortex showed greater activity for depressed participants compared with control participants during a rumination task (Cooney et al., 2010).

Depressive Rumination

There is a substantial body of literature linking rumination to depression. Cross sectionally, rumination is elevated in both currently and formerly depressed inpatients, which suggests that rumination is a stable trait factor (Watkins, 2008). Rumination is also concurrently associated with elevations in depressive symptoms among children, adolescents, college students, and adults (Abela & Hankin, 2008; Nolen-Hoeksema et al., 2008; Watkins, 2008). Furthermore, children, adolescents, and adults who engage in rumination when distressed demonstrate more severe and prolonged periods of depression and are more likely to develop depressive disorders (Abela & Hankin, 2011; Nolen-Hoeksema et al., 2008). For example, a recent meta-analysis (Aldao, Nolen-Hoeksema, & Schweizer, 2010) found large effect sizes for the relationship between rumination and depression. Longitudinally, rumination predicts increases in depressive symptoms (Hankin, 2008b; Rood, Roelofs, Bögels, & Alloy, 2010; Watkins, 2008) as well as the onset of a clinically significant depressive episode among never-depressed individuals (Abela & Hankin, 2011; Nolen-Hoeksema, Stice, Wade, & Bohon, 2007; Watkins, 2008) consistent with the risk factor model. In parsing out the specific effects of brooding and reflective pondering, researchers have found that brooding alone significantly predicts increases in depressive symptoms over time (Burwell & Shirk, 2007; Rood et al., 2010 for youth; Treynor et al., 2003 for adults). Reflective pondering, on the other hand, did not significantly predict changes in depression (Rood et al., 2010).

Findings in BD indicate that rumination is comparable to that seen in unipolar depression (Johnson, McKenzie, & McMurrich, 2008), or at a level that is intermediate between those with unipolar depression and healthy controls (Johnson et al., 2008; Thomas, Knowles, Tai, & Bentall, 2007). Rumination in BD is associated with greater depression, but not mania levels (Alloy et al., 2005). In addition, studies have found higher rumination levels among individuals at risk for BD (Johnson et al., 2008).

Studies of individuals with remitted BD have also found higher levels of rumination compared with healthy controls (Thomas et al., 2007), which provides additional support for the idea that rumination is a stable and enduring trait-like characteristic. Unfortunately, there is a relative dearth of longitudinal research on rumination in BD (Johnson et al., 2008), so it is unclear whether rumination represents a risk factor for BD.

Anxious Rumination and Worry

Anxious rumination has found support as a form of rumination that is distinct from depressive rumination (Rector, Antony, Laposa, Kocovski, & Swinson, 2008). A recent meta-analysis demonstrated medium to large effect sizes for the relationship between anxious rumination and anxiety among clinical and community samples of adults, as well as children, with different strengths applying to different anxiety disorders (Aldao et al., 2010). For anxiety disorders that feature repetitive thoughts related to personal concerns, such as SAD, GAD, OCD, and PTSD, these effect sizes were particularly large. In particular, GAD and OCD, which are characterized by not only persistent and repetitive thought, but also lack of cognitive control, demonstrated rumination scores that were comparable to those of mood disorders (Aldao et al., 2010). Conversely, panic disorder exhibited the smallest association with rumination. This is not surprising, given that some of the more defining features of panic disorder include physical arousal, rather than repetitive thoughts.

A line of research has explored a specific type of repetitive thought, known as post-event processing, in social anxiety. Individuals with social anxiety maintain a negative mental representation of themselves in social situations based upon how they believe they appear to others (Rapee & Heimberg, 1997). Following a social interaction, socially anxious individuals immediately conduct a postmortem of the event, recalling not only the mental representation of the self in that particular social situation but also memories of the self in other social situations. Because socially anxious individuals perceive the social situation as more negative than it actually was, they believe that the interaction reflected another social failure, thus preserving their beliefs of their own social inadequacy and thus perpetuating their social phobia (Clark & Wells, 1995). Both clinical and nonclinical socially anxious individuals reported higher levels of post-event processing compared with nonsocially anxious individuals (Brozovich & Heimberg, 2008). Findings indicate that socially anxious individuals engage in more post-event processing following a social interaction or speech task in the lab (Abbott & Rapee, 2004; Mellings & Alden, 2000; Perini, Abbott, & Rapee, 2006; Rachman, Grüter-Andrew, & Shafran, 2000). Finally, nonanxious college students who were instructed to ruminate following a similar lab-based socially evaluative task maintained their levels of state anxiety (Wong & Moulds, 2009).

Another line of research has examined the role of rumination in PTSD, as trauma-related rumination features prominently in this type of anxiety disorder (Elwood, Hahn, et al., 2009). More specifically, trauma-related rumination may involve thinking about the causes and consequences of the trauma, which prevents focusing on the events of the trauma itself (Elwood, Hahn, et al., 2009). Cross sectional studies have found associations between rumination and PTSD for several types of trauma, including physical and sexual assault, motor vehicle accidents, and disasters (Elwood, Hahn, et al., 2009). Prospective longitudinal analysis has shown that rumination shortly following a traumatic event predicts changes in PTSD symptoms over time (Elwood, Hahn, et al., 2009). It is important to note that the relation between rumination and PTSD is also present in children and adolescents (Ehlers, Mayou, & Bryant, 2003).

Similar to rumination, worry is another form of self-focused perseverative thought for negative events that provoke fear and anxiety due to perceived lack of control and uncertainty (Nolen-Hoeksema et al., 2008). Worry is an attempt at problem solving, such that individuals who worry try to anticipate all potential future outcomes, especially those that are negative and also highly unlikely. When these negative outcomes do not occur, fear is reduced and the worry is reinforced. Despite the substantial conceptual overlap with rumination, worry can be differentiated from rumination according to several factors. First, worry is focused on future threats, or on past events that have implications for future threats (Nolen-Hoeksema et al., 2008). Rumination, on the other hand, is related solely to past events. In addition, individuals who worry anticipate future outcomes to avoid present negative affect and cognitions. In contrast, rumination is actively focused on current negative affect and cognitions (Nolen-Hoeksema et al., 2008).

Anger Rumination

Anger rumination, which involves perseverative thought on angry affect and planning future aggressive acts, is associated with anger (Pedersen et al., 2011), as well as verbal (Anestis, Anestis, Selby, & Joiner, 2009), relational (Peled & Moretti, 2009), and physical aggression (Bushman,

Bonacci, Pedersen, Vasquez, & Miller, 2005; Bushman, 2002). Findings have indicated that both state and trait rumination are linked to aggression (Borders & Giancola, 2011). Whereas anger rumination is positively associated with anger and aggression, sadness rumination has been found to be a negative predictor of aggression (Peled & Moretti, 2009). It is hypothesized that sadness rumination involves a passive form of repetitive thought that is focused on the self, which leads to withdrawal behaviors. In contrast, anger rumination is a more action-oriented type of thought that is focused on others, which facilitates aggressive behavior and retaliation toward the offender (Peled & Moretti, 2009).

Cognitive Emotion Regulation Strategies

Cognitive emotion regulation strategies are cognitive responses to stressors that are used to mitigate emotional distress or modify the type of emotional experience (Aldao et al., 2010). Additionally, cognitive emotion regulation strategies can also be used to target the stressor itself. Unlike the maladaptive cognitive products reviewed to this point, distraction and reappraisal are two *adaptive* cognitive strategies that are shown to decrease negative emotional experience.

The medial prefrontal cortex has also been implicated in reappraisal and distraction, as this brain region is involved in appraising emotional stimuli in relation to the self and the environmental context (McRae et al., 2010). Lateral regions of the prefrontal cortex, which are closely related to cognitive control, are also recruited during these regulation strategies. Researchers have posited that activation of these regions may reflect the use of verbal working memory to generate and maintain the necessary cognitions to mitigate emotional distress (McRae et al., 2010). This hypothesis provides one potential connection between cognitive processing (e.g., working memory, EF) and products (e.g., reappraisal).

Distraction

Distraction is a form of emotion regulation that involves engaging in thoughts or behaviors to divert one's attention away from negative mood and instead toward more positive stimuli (Nolen-Hoeksema et al., 2008). Distraction can involve a change in internal focus, such as invoking pleasant thoughts or memories, or it can involve a change in external focus, such as engaging in a favorite hobby (Gross & Thompson, 2007). Distraction can be further divided according to two domains of strategies: active and passive. Active strategies require effort to attend to and engage in positive or neutral information that is unrelated to the negative stimulus (Webb, Miles, & Sheeran, 2012). For example, in a laboratory experiment, participants might be given explicit instructions to distract themselves by thinking about something that is unrelated to the negative emotional stimulus. Passive strategies, on the other hand, do not involve explicit instructions to distract, but still involve engagement in emotionally neutral or positive materials or tasks that are unrelated to the negative emotional stimulus (Webb, Miles et al., 2012). In utilizing distraction as an emotion regulation strategy to replace negative mood with a more neutral or positive mood, an individual avoids the potential for the negative mood to bias self-reflection or cognitive problem solving strategies (Nolen-Hoeksema, 1991).

Overall, findings indicate that distraction may serve as an important strategy for mitigating negative mood, however, studies examining the relationship between distraction and specific disorders are lacking. Meta-analytic findings suggest that distraction contributes to relatively large shifts in affect ($d = 0.46$; Augustine & Hemenover, 2009). A more recent review by Webb and colleages (2012) examined studies with nonclinical samples that employed experimental manipulation of emotion regulations strategies, such as distraction, and found variable effect sizes depending on the type of instructions that were provided. For instance, active distraction strategies demonstrated larger effect sizes ($d = 0.47$ when participants were asked to focus on positive material; $d = 0.38$ when asked to focus on neutral material) than passive distraction strategies ($d = 0.18$ when focusing on positive material; $d = 0.23$ when focusing on neutral material). The fact that these studies utilized experimental manipulation provides evidence that distraction may act as a causal protective factor that buffers against negative emotional experience.

A small body of research has explored the relationships between distraction and specific emotional disorders. A number of cross sectional studies with adults have found that distraction confers benefits for dysphoric individuals (e.g., Chang, 2004; Lam, Smith, Checkley, Rijsdijk, & Sham, 2003; Lyubomirsky & Nolen-Hoeksema, 1993); however other studies have not found this relationship (e.g., Just & Alloy, 1997; Nolen-Hoeksema & Morrow, 1993). Longitudinal studies with youth (e.g., Abela, Aydin, & Auerbach, 2006; Ziegert & Kistner, 2002) and adults (e.g., Huffziger & Kuehner, 2009) have found some support for the finding that distraction predicts decreases in depressive symptoms over time, but others have not been able to support these findings (e.g., Abela, Brozina, & Haigh, 2002; Abela, Vanderbilt, & Rochon, 2004).

Some studies have also examined remitted depressed patients (e.g., Huffziger & Kuehner, 2009; Joormann, Siemer, & Gotlib, 2007; Singer & Dobson, 2007). Overall, these studies have found that experimentally induced distraction strategies were as effective as other strategies, such as mindfulness, at improving mood. In addition, Huffziger and Kuehner (2009) found that a greater tendency to engage in distraction was associated with less negative mood and more positive mood across all experimental groups. Moreover, Huffziger, Reinhard, and Kuehner (2009) also found that distraction in formerly depressed inpatients predicted fewer depressive symptoms over time.

There is a lack of research on the association between distraction and other types of disorders. One study by Ehring, Fuchs, and Kläsener (2009) conducted an experimental manipulation of distraction among individuals with PTSD and found that distraction led to decreases in negative mood and also a decrease in the frequency and distress of intrusive memories. A few studies have examined the relationship between distraction and anger. Ray, Wilhelm, and Gross (2008) and Denson, Moulds, and Grisham (2012) examined a nonclinical undergraduate sample and found that distraction significantly reduced anger. Moreover, Bushman et al. (2005) and Rusting and Nolen-Hoeksema (1998) found that distraction was not only associated with reports of decreased anger, but also better problem solving abilities. These experimental manipulation strategies lend further support to the causal role of distraction in reducing the impact of negative affect in various forms of psychopathology.

Cognitive Reappraisal

Cognitive reappraisal refers to the ability to change how one thinks about a situation or about one's capacity to manage the demands of a situation to alter its emotional significance (Gross & Thompson, 2007). Reappraisal can act upon different aspects of the situation (Webb, Miles, et al., 2012). One could reinterpret the cause or context of the situation that is evoking the emotion. For instance, Hajcak and Nieuwenhuis (2006) instructed participants to "Come up with a less negative interpretation of the picture content (e.g., a bloody crime scene could be seen as the place where a murder investigation was finally solved)" (p. 292). One could adopt a more objective or third-person perspective.

As with distraction, reappraisal may also serve as an important strategy for mitigating negative mood; however, studies examining the relationship between reappraisal and specific disorders is still in its infancy. Meta-analytic findings for experimental manipulation of emotion regulation strategies, such as reappraisal, have found a small-to-medium sized effect of reappraisal on emotional responding ($d = 0.36$; Webb, Miles, et al., 2012). These researchers further examined this effect by considering the target of the reappraisal strategy. Reappraising the cause or context of the situation had a small-to-medium effect on emotional response ($d = 0.45$), distancing oneself or taking a third person perspective had a small-to-medium size effect ($d = 0.36$), and reappraising the resulting emotional response had a small effect ($d = 0.23$).

Although a substantial body of literature has examined the relationship between reappraisal and various types of affect (e.g., general negative affect, sadness, anger) fewer studies have considered how reappraisal may relate to the more extreme and severe forms of affect that are implicated in psychopathology. A meta-analysis of reappraisal found that self-reported reappraisal was negatively associated with psychopathological symptoms overall ($d = -0.28$; Aldao et al., 2010). In the case of depression, specifically, trait reappraisal is associated with lower symptom levels (Gross & John, 2003) and fewer depressive episodes (Garnefski, Kraaij, & Spinhoven, 2001; Garnefski & Kraaij, 2006; Kraaij, Pruymboom, & Garnefski, 2002).

Reappraisal manipulations in a laboratory setting have also been demonstrated as an effective strategy for reducing anxiety in college undergraduates (Hofmann, Heering, Sawyer, & Asnaani, 2009) and for decreasing negative emotion in children and adolescents diagnosed with GAD, separation anxiety, and SAD (Carthy, Horesh, Apter, Edge, & Gross, 2010). Reappraisal was also associated with lesser total PTSD severity among military service veterans diagnosed with PTSD (Boden, Bonn-Miller, Kashdan, Alvarez, & Gross, 2012). Conversely, less frequent use of cognitive reappraisal was associated with higher levels of PTSD symptom severity (Eftekhari, Zoellner, & Vigil, 2009; Ehring & Quack, 2010).

A moderate reduction in anger was shown for treatment programs that utilized cognitive restructuring, a correlate of reappraisal (DiGiuseppe & Tafrate, 2003). Ray et al. (2008) and Denson et al. (2012) examined a nonclinical undergraduate sample and found that reappraisal of an anger-eliciting event significantly reduced anger. Among outpatient participants with schizophrenia and schizoaffective disorder, those who were instructed to reappraise reported experiencing less sadness and general negative affect (Perry & Henry, 2012). However, there may be no trait differences in tendency to reappraise, as individuals with schizophrenia did not differ from control participants in their use of reappraisal strategies (Badcock, 2010; Henry, Rendell, Green, McDonald, & O'Donnell, 2008).

As with distraction, experimental manipulation of reappraisal, as well as treatment interventions that employ reappraisal, this type of cognitive emotion regulation strategy may be causally related to emotional distress and psychopathology.

Gender, Cultural, and Ethnic Differences and Considerations

A preponderance of studies examining demographic differences in cognitive products have focused largely on gender, as rates of internalizing psychopathology are markedly higher in females, whereas externalizing psychopathology is more prevalent in males (Zahn-Waxler, Crick, Shirtcliff, & Woods, 2006). Studies of gender differences in negative inferential styles, for instance, have found that females report more negative inferential styles than males, which might explain the fact that females are more likely to develop depression in adolescence than males (Hankin & Abramson, 2002; Mezulis, Abramson, Hyde, & Hankin, 2004). In addition, studies have found that negative attributional style was only associated with elevations in depressive symptoms at high levels of negative life events for males (e.g., Hankin, Abramson, & Siler, 2001; Stone, Gibb, & Coles, 2009). Among females, however, negative attributional style was associated with depressive symptom elevation even at low levels of negative events. Therefore, a negative inferential style may both mediate and moderate gender differences in depression. There is a relative lack of studies examining gender differences for other types of cognitive styles. A few studies have found that males exhibit more dysfunctional attitudes compared with females (Haeffel et al., 2003; Hankin, 2009). In addition, some studies have identified gender differences in hostile attribution biases, such that boys demonstrate hostile attribution bias for instrumental provocation situations and girls exhibiting this bias for relational provocation (Crick & Dodge, 1994; Crick et al., 2002).

There are also notable gender differences in repetitive negative thought, such that females report higher levels of depressive rumination compared with men (Hankin, 2008b; Susan Nolen-Hoeksema, 2012; Rood et al., 2010), whereas males may engage in more anger rumination compared with women (e.g., Rusting & Nolen-Hoeksema, 1998). As with negative inferential style, it has been suggested that the gender difference in depressive rumination, in particular, partially accounts for the gender difference in depression rates among females and males (Hankin, Wetter, & Cheely, 2008; Hankin, 2009; Watkins, 2008). However, some studies, especially with children and early adolescents, have not found sex differences in rumination (Abela, Brozina, & Haigh, 2002; Abela, McGirr, & Skitch, 2007; Abela & Hankin, 2011; Abela, Vanderbilt, & Rochon, 2004). This underscores the point that consistent sex differences in response styles, such as rumination, may not develop until early to middle adolescence (Hankin et al., 2008; Watkins, 2008).

There is also some evidence for gender differences in cognitive emotion regulation strategies. According to a review by Nolen-Hoeksema (2012), women were more likely than men to report using reappraisal and distraction. Some researchers (e.g., Barrett, Lane, Sechrest, & Schwartz, 2000) have posited that men may engage in more automatic, subconscious emotion regulation, and as a result may not report the use of conscious, language-based strategies, such as reappraisal or distraction. In line with this finding, a neuroimaging study by McRae and colleagues (2008) suggests that men may indeed engage in reappraisal; however results indicate that they do so more automatically and with less mental effort compared with women.

Compared with research on gender differences in cognitive products, relatively few studies have explored cultural and ethnic differences in these constructs. There is evidence showing that predictive associations are maintained across different cultural and ethnic groups. For example, interactions between negative cognitive styles (e.g., inferential style and dysfunctional attitudes) and stressful life events predict depressive symptoms in youth samples of rural and urban regions of China (Abela et al., 2011) as well as youth in Spain (Calvete, Villardón, & Estévez, 2008), the same as found in the United States. Furthermore, early maladaptive schemas are risk factors for the development of depression (Calvete, Orue, & Hankin, 2012), anxiety (Cámara & Calvete, 2011), and aggression (Calvete, 2008) in Spanish youth. While predictive associations seem to be similar across cultural groups, there is also evidence for mean level differences in cognitive influences. For example, the positivity bias (i.e., stronger positive relative to negative attributional style) is higher among individuals from Western, individualistic cultures relative to East Asian, collectivistic cultures (Mezulis et al., 2004). Additional research that directly compares these constructs across cultures will help to elucidate potential cultural and ethnic differences.

DISCUSSION

Summary: Empirical Status of Cognitive Products and Processes in the Development of Psychopathology

There are several main points to emphasize based upon our review of the literature. First, it is clear that the preponderance of evidence shows that cognitive products and

processes are associated, at least concurrently, with many prevalent psychopathologies in children, adolescents, and adults (Table 8.8). At this point and with the current state of knowledge, the field generally does not need more cross sectional, case control designs comparing a group with one specific disorder to healthy controls (especially adults, as much of the literature, particularly with cognitive processes, has used almost exclusive adult samples). The cross sectional case-control design only addresses the question of whether there is a difference in cognitive risk between groups, and that question has been satisfactorily answered in the affirmative, at least for disorders, cognition, and age groups reviewed herein. There is value for cross sectional work in new areas (e.g., preschool psychopathology). At a minimum, future research examining the cognitive products and processes reviewed here should utilize longitudinal designs to better disambiguate which of several logical conceptual models (e.g., cause, consequence, correlate; see earlier for expanded discussion) best characterizes how these cognitive influences relate to developmental trajectories of psychopathology (onset, maintenance, desistance) over the life-course.

Second, there is need for research using carefully selected age-relevant samples that are thoughtfully chosen to investigate developmentally oriented questions. As just noted, most of the process studies have used adult samples, yet such research cannot easily address developmentally sensitive questions relevant for understanding onset, course, and trajectory of disorders because many disorders have child or adolescent onsets and then exhibit a chronic pattern, especially in adulthood. As such, exclusive use of adult samples, which likely comprises an unknown admixture of some new onsets alongside mostly recurrences (and it would be important to assess and investigate whether these are first recurrences or multiple), does not significantly advance knowledge on the role of cognitive influences in developmental trajectories of psychopathology. On the other hand, very few studies have examined cognitive influences with preschool-age children; developmentally sensitive and age-appropriate measures of cognitive products and processes can be used to examine associations with prevalent preschool psychopathologies (Egger & Angold, 2006). While our review shows that cognitive products, in particular, and likely cognitive processes, are associated with common psychopathologies in children and adolescents to an equal magnitude as found in adults, often the ages of samples in these studies employed relatively wide age ranges (e.g., 9–18 year olds) that may not carefully match developmental questions. Future research would benefit from using tighter age ranges that are thoughtfully connected to developmentally sensitive questions.

Last, there likely exist meaningful developmental patterns in how cognitive risks operate over time to influence the development of psychopathology, yet it is not entirely clear how various developmental factors (e.g., biological, cognitive, and emotional development; changes in social contexts—peers, parents) affect this process. The extant data, as reviewed earlier, suggest that cognitive products and processes may broadly apply as risks to multiple common psychopathologies across the life span, including children, early adolescents, adolescents, and adults. Yet at the same time, it is likely that much change occurs with respect to these cognitive risks throughout childhood and adolescence. In particular, it is likely that accumulating environmental experience (e.g., stressful life events) and known changes in cognitive, emotional, and biological influences across development contribute to (1) the emergence, and developmental origins, of these cognitive influences and when they function to confer risk to development of psychopathologies; (2) greater stabilization of cognitive influences into more enduring, trait-like risks over time; and (3) enhanced interrelatedness and consolidation among the different cognitive products and processes. In sum, there is still a need for research examining cognitive products and processes in the development of psychopathology across the life span. In the sections that follow, we discuss developmentally relevant areas for advancing knowledge of cognitive risks to psychopathology.

Developmental Considerations

Cognitive risks to the development of psychopathology, by definition and theory, are believed to reflect stable individual differences, certainly by adulthood. However, the age when cognitive products and processes emerge as stable risks for psychopathology, and the extent to which they represent trait-like risk processes over the life span, especially in childhood and adolescence, remains largely unknown. Addressing these questions is essential for both basic developmental clinical scientific knowledge and for informing translational applications. Understanding when and how cognitive products and processes emerge as stable risks to various psychopathologies can potentially inform when to implement optimal, developmentally sensitive interventions and provide etiologically valuable clues to better understand the established developmental epidemiological patterns (e.g., first onset, maintenance, recurrence, desistance) in various prevalent psychopathologies.

Moreover, and as we discuss in greater detail later, it may be that different underlying *mechanisms* lead to various psychopathologies at different developmental periods.

TABLE 8.8 Summary of Findings

	Executive function	Attention	Memory	Cognitive styles	Repetitive negative thought	Cognitive emotion regulation strategies
Depression	• Broad impairment across all aspects of EF	• Mixed evidence for impaired sustained attention • Little research on selective attention, but appears intact • Little research on divided attention, but may be impaired • Biased attention toward negative stimuli	• Impaired episodic memory • Impaired autobiographical memory • Little research on semantic memory, but appears to be intact	• Negative inferential style, dysfunctional attitudes, and early maladaptive schemas (e.g., disconnection/ rejection, impaired autonomy, other-directedness) linked to symptoms and episodes of depression; mixed evidence for remitted depression • Very little evidence for link to hostile attribution bias • No evidence for looming maladaptive style	• Depressive rumination, especially brooding linked to symptoms and episodes of depression	• Distraction and reappraisal linked to lower levels of negative affect • Mixed findings linking distraction and reappraisal to dysphoria and depressive symptoms
Bipolar disorder	• Broad impairment across all aspects of EF	• Impaired sustained attention • Little research on selective attention • Little research on divided attention, but may be impaired • Little research on biased attention, but may be bias toward negative and manic stimuli	• Impaired episodic memory • Intact semantic memory • Little research on autobiographical memory, but may be impaired	• Negative inferential style linked to depression and mania • Positive inferential style linked to mania • Early maladaptive schema (e.g., impaired limits) linked to BD • No evidence for hostile attribution bias or looming maladaptive style	• Small body of evidence linking depressive rumination to depression in BD	
Anxiety	• Impairments across most aspects of EF for OCD and PTSD • Little research on other anxiety disorders	• Little research on sustained or selective attention • Little research on divided attention, but may be impaired • Biased attention toward negative stimuli	• Impaired episodic memory in OCD and PTSD • Impaired autobiographical memory in PTSD • Little research on other anxiety disorders	• Some evidence for link between negative inferential style and comorbid depression and anxiety, but not anxiety alone (PTSD is an exception) • Early maladaptive schemas (e.g., impaired autonomy) linked to anxiety • Strong link to looming maladaptive style	• Anxious rumination linked primarily to SAD, GAD, OCD, PTSD • Support for postevent processing, a type of anxious rumination, in SAD • Little evidence for link to PD	• Little evidence linking distraction to decreases in negative mood in PTSD, only • Reappraisal linked to deceases in anxiety

Schizophrenia	• Broad impairment across all aspects of EF	• Impaired sustained attention • Visual selective attention appears largely intact (overall response slowing only). Auditory selective attention may be impaired • Little research on divided attention, but may be impaired • Little research on biased attention, but may be bias toward disorder-specific stimuli (e.g., paranoia words)	• Impaired episodic memory • Impaired semantic memory • Impaired autobiographical memory	• Persecutory delusions associated with attributions of negative events to external personal causes as well as hostile attribution bias • Some evidence showing link to concern about self-efficacy and performance • No evidence for looming maladaptive style	• No evidence for rumination in schizophrenia	• No evidence for distraction or reappraisal in schizophrenia
ADHD/ externalizing	• Broad impairment across all aspects of EF	• Impaired sustained attention • Selective attention appears largely intact (overall response slowing only) • Little research on divided attention, but may be impaired • Little research on biased attention	• Impaired verbal episodic memory, but nonverbal episodic memory appears to be intact • May be small impairments in semantic memory • Little research on autobiographical memory	• Some evidence for negative inferential style in ADHD, includes a controllability dimension • Early maladaptive schemas (e.g., entitlement/grandiosity) linked to aggression • Hostile attribution bias linked to aggression and ADHD • No evidence for looming maladaptive style	• Anger rumination linked to aggression	• Distraction and reappraisal linked to decreases in angry mood

In particular, two logical hypotheses are important to consider. First, it may be that the mechanisms fundamentally implicated in products and processes only emerge and work to contribute to development of psychopathologies shortly before these disorders typically onset. Alternatively, the various cognitive influences may exist and function as risks earlier, but remain latent until activated (e.g., by stressors, for those cognitive influences postulated to operate per a vulnerability-stress model). In other words, a critical, but relatively uninvestigated question, is *why* various cognitive risks predict developmental patterns of psychopathology (e.g., first onsets) and *when* these phenomena are most likely to occur. The ensuing discussion focuses on theoretical possibilities and some key empirical evidence regarding developmental influences, specifically emergence and origins, then stabilization, and finally the structure and eventual consolidation, of cognitive influences.

Emergence of Cognitive Products

Historically, since the original theorizing on cognitive theories of psychopathology, there has been considerable speculation, and some empirical research, regarding which developmental stage and age period best characterize when cognitive products emerge as potent risks for the development of psychopathology (e.g., Gibb & Coles, 2005; Hankin et al., 2009; Rutter, 1987). For example, from the perspective of Beck's cognitive theory, it is hypothesized that schema are not consolidated until adolescence or even early adulthood because it has been postulated that repeated learning experiences need to reinforce the schemas to be actively operating and lead to symptoms (e.g., Hammen & Zupan, 1984). Also earlier theorizing for the hopelessness theory (Abramson et al., 1989) postulated that a depressogenic attributional style only emerges during the transition from childhood to adolescence when children acquire the ability to engage in abstract reasoning and formal operational thought (e.g., Nolen-Hoeksema, Girgus, & Seligman, 1992).

In seeking to explain mechanisms that may underlie potential developmental changes in cognitive products based on these early conceptual speculations, researchers have drawn from a wide variety of findings in the cognitive development literature—particularly those pertaining to middle childhood. For example, during middle childhood, children start to develop a more stable and less concrete sense of self (Rholes, Blackwell, Jordan, & Walters, 1980). Their self-views become increasingly differentiated as they shift their focus from concrete, behavioral characteristics in early childhood to relatively more personality trait-like characteristics in middle childhood to more abstract psychological constructs during adolescence (e.g., Harter, 1990). During this developmental period, children also become less here-and-now oriented (Shirk, 1988) and more likely to integrate past experience into working knowledge in a manner that informs interpretations and predictions (Rholes et al., 1980). Whereas very young children have a rudimentary understanding of causality (e.g., Oakes, 1994), middle childhood is when children use stable personality traits increasingly to explain their behavior (e.g., Corrigan, 1995).

Some early empirical research examined the hypothesis that cognitive products (mostly a negative attributional style, as the most theorized and researched) emerge during the transition from middle childhood to early adolescence, based on the view that it is necessary that concrete operations be present for negative attributions to be made about explaining the cause of negative events. Results from two studies in particular provide the most compelling support for this early hypothesis based on necessary cognitive developmental maturity requirements in late childhood (Nolen-Hoeksema et al., 1992; Turner & Cole, 1994); these studies suggest that a depressogenic attributional style interacted with negative events to predict higher levels of depressive symptoms in later childhood/early adolescence, but not earlier in childhood. However, these early studies tended to focus relatively narrowly on only one particular cognitive risk (e.g., negative attributional style) and tended to investigate age of emergence with psychometrically poor measures, which obviously affect ensuing conclusions. Since these initial investigations, more recent studies using more reliable and developmentally sensitive measures have shown that cognitive products, such as a negative attributional style, predict increases in depressive symptoms much earlier (e.g., by age 6, Conley et al., 2001; age 8, Abela, 2001) than previously thought and than what was originally theoretically expected based on cognitive maturity hypotheses.

Presently, the developmental period and age by which cognitive products emerge is not clearly established. Our review indicates that a negative cognitive style predicts depressive symptoms as early as age 6 (Conley et al., 2001), dysfunctional attitudes by age 6 (Abela & Skitch, 2007) in offspring of depressed mothers, and rumination by age 6 (Abela, Hankin, Sheshko, Fishman, & Stolow, 2012) in offspring of depressed mothers; age 8 in normative sample, (Lopez, Felton, Driscoll, & Kistner, 2012). However, these findings should be interpreted tentatively because there have been insufficient studies that have focused on the

earliest ages by which these cognitive products predict various psychopathological outcomes, and the earliest prediction may vary depending on the form of psychopathology examined (e.g., separation anxiety symptoms with earlier modal age of onset versus depression or PTSD). Also, developmentally sensitive and reliable measures are needed to rigorously examine emergence of these risks in earlier ages (e.g., preschoolers). Last, there is a paucity of theory to suggest when and why particular cognitive products would emerge as contributing factors conferring risk to different psychopathologies. (Note, there is some theory and evidence regarding developmental origins and precursors of these cognitive products, and such work, reviewed later, has relevance for understanding the emergence of these risks.)

Developmental theory and research on origins and emergence for hostile attributional bias has been less controversial. According to developmental literature, hostile attribution bias serves as the default attributional style in prevocational situations and is present very early in life (Dodge, 2006). Hostile attributions follow from a simple assumption that an act that brings about a negative outcome for the self must logically originate from an actor with a negative intent (Dodge, 2006). This rigid association between negative outcome and negative intent becomes more flexible as a result of cognitive development that begins at about age three or four. It is during this time that young children acquire the capacity to understand that others' mental states are different from our own, and they can make correct inferences about the content of the mental states (e.g., intentions and beliefs) of others (Couture, Penn, & Roberts, 2006).

These inferences serve an adaptive purpose by allowing individuals to predict and explain others' behavior in a social context (Lee, Farrow, Spence, & Woodruff, 2004). In the specific case of negative outcomes, identification and interpretation of social cues that signal that the actor may have acted without intent or with a benign intent, instead of malevolently, is a particularly important (Dodge, 2006), albeit more complicated, formal operation. Early adolescence is another key developmental period that facilitates the ability to infer lack of intent or benign intent, as this stage of cognitive development is characterized by the ability to generate alternatives and consider hypothetical possibilities (Dodge, 2006). Over time, the ability to interpret ambiguous social cues as nonintentional facilitates the development of a stable pattern of inferring benign intent, especially in ambiguous situations. Therefore, a hostile attribution bias evolves from an individual not acquiring a benign attributional style and instead continuing to match intent with outcome (Dodge, 2006).

Emergence of Cognitive Processes

While much is known about typical (and to some extent abnormal) development of cognitive processes, little is known about when cognitive processes emerge as risks for the development of psychopathology. Unlike cognitive products, which as discussed above are hypothesized to emerge only after particular stages of development, in typically developing children cognitive processes develop continuously throughout childhood, and in some cases into early adulthood. EF has a particularly protracted developmental course, following the protracted development of prefrontal cortex. Some early developmental milestones are reached during the preschool years (e.g., the ability to switch between two simple tasks rather than perseverating on the first task (Munakata, Chatham, & Snyder, 2012a). Throughout early and middle childhood, there is continued quantitative (e.g., ability to switch between tasks more efficiently), and qualitative (e.g., shift from reactive to proactive control strategies) development (Munakata et al., 2012a). Unlike some other cognitive abilities, which are relatively mature by the end of middle childhood, EF continues to develop through adolescence and even into early adulthood (e.g., Huizinga, Dolan, & van der Molen, 2006), and then declines in older adulthood (e.g., Buckner, 2004).

In contrast to EF, attention and memory processes develop relatively early, though they continue to develop throughout childhood. Infants already have the ability to selectively attend to particular stimuli in some circumstances (Atkinson & Braddick, 2012). Selective, divided, and sustained attention abilities continue to develop through middle childhood when they generally reach adult levels (e.g., Waszak, Li, & Hommel, 2010), although some development may continue in adolescence (e.g., McAvinue et al., 2012). As with attention, even infants have impressive memory abilities (Bauer, 2007), although the ability to retrieve specific episodic memories continues to improve through middle childhood (e.g., see Ghetti & Bunge, 2012 for review), and semantic memories continue to accrue throughout the life span. Like EF, age-related declines in memory are common (Buckner, 2004).

Given these normal patterns of development, there are several logical possibilities as to when these cognitive processes might emerge as psychopathology risks. First, deficits in these processes might be present from early in development and serve as risks throughout the life span.

This pattern is consistent with the evidence in ADHD, which is associated with poor EF from preschool to adulthood. There has been little research with young children in other areas, but many cognitive deficits are similarly associated with multiple forms of psychopathology in childhood, adolescence, and adulthood, suggesting that cognitive process risks may be relatively stable across the life span. Second, cognitive deficits could be present from early in development, but only become associated with psychopathology in the presence of other risk factors or developmental vulnerability periods for psychopathology. Detecting this pattern requires long-term prospective longitudinal studies beginning in early childhood. Finally, cognitive deficits could emerge later in development, either because of neurodevelopmental abnormalities or neurodegenerative processes, as discussed later.

Developmental Origins of Cognitive Risks. In addition to knowing when cognitive influences emerge as salient predictors of psychopathology, an important and related question concerns the developmental origins of these cognitive risks. While many precursors have been postulated and examined, here we consider some of the more consistently conceptualized and examined factors, including negative parenting and social modeling, negative life events including abuse and trauma, and genetics.

Parenting. A prominent hypothesis is that cognitive products and processes may arise from maladaptive parenting practices. Based on a cognitive-developmental framework, parenting behaviors convey information to the child which may be internalized and subsequently contribute to the construction of beliefs and related processes (Bruce et al., 2006). Positive aspects of parenting (e.g., high levels of warmth, acceptance, autonomy promotion, consistency, and positive reinforcement) would be expected to contribute to the development of positive self-beliefs, whereas negative forms of parenting (e.g., high levels of criticism, rejection, control, and inconsistency) likely contribute to the formation of negative self-views and related processes (e.g., Beck, 1967; Young, 1999).

Several cross sectional studies support the association between maladaptive parenting practices and cognitive products. For example, regarding Beck's cognitive theory, high levels of parental criticism, indifference, and control and low levels of parental acceptance and care are associated with dysfunctional attitudes and cognitive distortions in youth (e.g., Bruce et al., 2006; Garber & Flynn, 2001; Liu, 2003) as well as a negative self-concept (e.g., Bruce et al., 2006; Liu, 2003). Similarly, high levels of parental criticism and control and low levels of parental care and acceptance correlate with a depressogenic attributional style in youth (e.g., Bruce et al., 2006; Garber & Flynn, 2001). While comparatively less research has extended this line of inquiry into developmental origins of cognitive processes, one study demonstrated that coded observations of negative parenting styles (authoritarian) and behaviors (criticism, negative affect) were associated with youths' attentional biases to negative emotion, especially angry faces, in two independent samples (Gulley, Oppenheimer, & Hankin, 2013).

The few prospective studies to examine parental influences as precursors to development of cognitive products have been supportive. Maternal reports of high rejection and restrictiveness, when children were age five, prospectively predicted youths' self-criticism at age twelve (Koestner, Zuroff, & Powers, 1991). Also, observations of maternal feedback to child failure as well as temperament (from infancy to age 11, (Mezulis, Hyde, & Abramson, 2006); and from age 11 to 15, (Mezulis, Funasaki, & Hyde, 2011) along with maternal cognitive style (from age 11 to 15; Mezulis et al., 2011) predicted development of youths' cognitive style. Last, maternal encouragement of emotion expression in daughters predicted higher rumination levels from age 11 to 15 (Cox, Mezulis, & Hyde, 2010).

What mechanisms might explain this relation between negative parenting and youths' cognitive risks? Mostly, social modeling processes have been evaluated. Evidence for this proposed process is mixed. More consistent evidence has accumulated for one variation of the modeling hypothesis, in which children model feedback communicated to them by their parents about events in the children's own lives rather than modeling their parents' own negative cognitions (e.g., Garber & Flynn, 2001; Mezulis et al., 2011, 2006). Less evidence exists for the modeling variant that children learn and adopt negative cognitions by observing their parents' own negative styles concerning their parents' own behavior. One study showed that children's attributional styles correlated with those of their mothers, but not their fathers (Seligman et al., 1984), whereas others have failed to replicate these findings (e.g., Garber & Flynn, 2001).

Negative Life Events. Second, certain types of negative life events, including (1) repeated exposure to stressors in multiple and interacting domains (e.g., family conflict, divorce, poverty) and (2) traumatic events and maltreatment, may contribute as salient precursors in the development of cognitive products and processes. Accumulation of chronic exposure to negative events can lead to formation of negative cognitions that become deeply

ingrained in self-structures (e.g., Rose & Abramson, 1992). Prospective research has supported this hypothesis with children's experience of negative events (Garber & Flynn, 1998) as well as various facets of family disturbance (i.e., divorce, abandonment, parental death, interparental conflict; Rudolph, Kurlakowsky, & Conley, 2001). With respect to trauma and maltreatment, experience of these more adverse negative environments has been shown to associate with cognitive products in adults (e.g., Gibb et al., 2001; Hankin, 2005) and children (e.g., Dodge, Pettit, Bates, & Valente, 1995; Gibb et al., 2006) as well as various attentional (e.g., Pollak & Tolley-Schell, 2003) and memory (Parsons & Ressler, 2013) processes.

These robust associations between traumatic events and cognitive risks may occur for at least two reasons. First, after trauma exposure, youth attempt to understand the causes, meaning, and consequences of such events; especially when such events are chronic (recurrent across time) and pervasive (recurrent across situations), it is more likely that the child will develop stable, enduring cognitive beliefs to explain the maltreatment and to better predict and control future adverse events (Rose & Abramson, 1992). Formation of negative cognitive products may be particularly likely when the child is emotionally maltreated, as the abuser is directly providing the child with negative information (e.g., you're stupid, lazy) that can directly become cognitive products (e.g., attributions, dysfunctional attitudes, early maladaptive schemas). Second, Pollak's theory of experience-dependent affective learning (2003) proposes that children are biologically prepared for emotion, and the formation of such systems depends, at least to a certain extent, upon salient environment inputs. Abusive experiences are associated with threatening, inconsistent, or excessive emotional signals, which in turn contribute to enhanced threat detection and attentional allocation to predictive environmental and emotion cues (e.g., parents' angry face can probabilistically portend greater likelihood of physical abuse). What started as an initially adaptive learning process to detect threat to keep the child safe can extend into the formation of biased processing of social and emotional information across many contexts that are no longer objectively threatening (e.g., Pollak, Vardi, Bechner, & Curtin, 2005), and in turn, contribute to psychopathologies (Gulley et al., 2013; Shackman, Shackman, & Pollak, 2007).

Genetic and Biological Influences. Genetic, as well as other neural and biological influences, may serve as developmental precursors to the emergence of cognitive risks. First, significant associations have been observed between molecular genetics and cognitive products (e.g., rumination; Beevers, Wells, & McGeary, 2009; Hilt, Sander, Nolen-Hoeksema, & Simen, 2007) and processes (e.g., attention bias to negative emotion; Gibb et al., 2013). Similarly, behavioral genetic research has demonstrated that cognitive risks, such as a negative attributional style (Lau, Rijsdijk, & Eley, 2006), are moderately heritable. Furthermore, there is also evidence that some deficits in EF, memory and attention may be a particular form of genetic risk factor: endophenotypes (Gottesman & Gould, 2003). To be considered an endophenotype, a characteristic must be (1) associated with illness in the population, (2) heritable, (3) primarily state-independent (manifest even when illness symptoms are not present), (4) cosegregate with illness within families, and (5) be present in unaffected family members at a greater rate than in the general population. Criteria 1 and 2 are met for most cognitive processes across most disorders, since cognitive deficits are associated with mental illness as discussed in the literature review, and cognitive processes are largely heritable (Friedman et al., 2008). Moreover, there is evidence for criterion 3 in many cases—for example, cognitive deficits are present in individuals with MDD in remission and euthymic BD. Finally, criteria 4 and 5 are also met in many cases, with evidence that unaffected family members of individuals with schizophrenia, BD, OCD, and PTSD have cognitive function which is more impaired than the general population but less impaired than their affected family members. While these data showing associations between genetic factors and cognitive risks are consistent with a developmental origins hypothesis, the cascade of mechanisms connecting initial genetic risk (e.g., polymorphic variation in particular candidate genes) to later individual differences in cognitive products and processes are unknown and in need of theoretical and empirical investigation.

Second, regardless of whether cognitive factors are a cause, correlate, or consequence of psychopathology, *neurodevelopmental* and *neurodegenerative* mechanisms may play a role. Neurodevelopmental processes involve an abnormal unfolding of brain development, while neurodegenerative processes involve loss of neural function over time. While neurodevelopmental processes are posited to play a role in many disorders, the lack of large prospective studies starting early in life has hampered efforts to test these hypotheses and determine the neural processes involved. Neurodevelopmental processes involved in psychopathology are hypothesized to be driven by both genetic and early environmental influences (e.g., prenatal exposure to toxins or infection, postnatal stress) and to

take many forms, including alterations in neurogenesis and apoptosis, the formation and pruning of synaptic connections, and receptor expression (e.g., Rappaport, Giedd, & Gogtay, 2012).

Perturbations in neurodevelopment could take the form of delays in normal developmental processes (e.g., children with ADHD undergo the same sequence of cortical maturation as healthy children, but the timing is delayed; Shaw et al., 2012), or abnormal developmental processes (e.g., atypical patterns of white matter connectivity in neonates at genetic risk for schizophrenia; Shi et al., 2012). While cognitive impairments are presumed to be consequences of neurodevelopmental abnormalities in neurodevelopmental models, links between neurodevelopment and psychopathology are potentially more complex. Early neurodevelopmental abnormalities could be either causes or correlates of psychopathology, while perturbations in neurodevelopment after disorder onset could also conceivably be a consequence of psychopathology, via either direct alterations in neurobiology or indirectly by altering the individual's environment and experiences in a way that changes the course of development (e.g., transactional model).

The most common neurodegenerative model applied to cognitive deficits associated with psychopathology centers around disordered stress and immune responses (e.g., Conrad, 2008). Since chronic stress and elevated cortisol have been linked to many forms of psychopathology (e.g., adult depression; Stetler & Miller, 2011; schizophrenia; Walker, Mittal, & Tessner, 2008), this is a plausible pathway for neurodegeneration and subsequent cognitive deficits associated with psychopathology. Interestingly, abnormally low levels of cortisol (e.g., in PTSD; Morris, Compas, & Garber, 2012) may also lead to neurodegeneration, although the mechanisms need specification (Conrad, 2008).

Neurodegenerative processes could be a consequence of psychopathology (e.g., psychopathology leads to disordered stress response, which leads to neurodegeneration). For example, a meta-analysis found progressive loss of grey matter in the prefrontal cortex and temporal lobe in individuals with schizophrenia, especially during the first episode, suggesting that the onset of schizophrenia triggers a neurodegenerative process (Vita et al., 2012). However, neurodegenerative processes could also be a cause (e.g., chronic stress leads to neurodegeneration which leads to psychopathology) or a correlate (e.g., chronic stress leads independently to both psychopathology and neurodegenerative processes), or the result of a positive feedback loop between these processes (Conrad, 2008). However, in all of these cases cognitive deficits are presumed to be a consequence of the neurodegenerative processes. Since glucocorticoid receptors are highly expressed in the hippocampus and prefrontal cortex, neurodegenerative processes may have the greatest impact on memory and EF (e.g., Hinkelmann et al., 2009), perhaps accounting for their widespread impairment across disorders.

Cognitive Consequences. While not exactly a factor that is contributing as a precursor, per se, to cognitive risk, researchers have hypothesized that experiencing sustained psychopathology may further enhance the development of cognitive products and processes that persist after the peak of symptoms decline (i.e., cognitive scar). From this perspective, a youth's initial psychiatric episode may be caused by factors other than cognitive risks (e.g., a youth's coping abilities are overwhelmed following the experience of a severe stressor). As a consequence of and following the onset of the episode, the individual develops cognitive risks to the recurrence of psychopathology.

This exacerbation of cognitive risk into a more enduring cognitive vulnerability can occur through several (not necessarily exhaustive) pathways. First, youth who develop psychopathology frequently exhibit other noncognitive risk factors, such as poor academic performance and impaired peer relations, and these failures and risks may lead youth to the development of particular cognitive products (e.g., beliefs about low abilities; lack of control over important outcomes) and processes (e.g., greater attention to, encoding of, and memory for such negative experiences). Second and related, experiencing psychopathology symptoms may facilitate access to negative memories and thoughts due to the priming effects of mood on cognition (Bower, 1981). These negative cognitions can be encapsulated and coalesce into enduring products and processes, especially if they persist over an extended period of time and while essential self-concepts and thinking styles are under construction and developing (e.g., middle childhood; early adolescence). Finally, there can be dynamic, transactional relations between the stressful life events that may have triggered the onset of the disorder, and in turn, youth may behave in ways that reinforce the development of the cognitive risks. For example, a child with poor social skills, who consequently encounters rejection, may learn to expect such rejection. Subsequent behavior (e.g., withdrawing from social activity) may contribute to further social rejection, and consequently reinforce and strengthen the developing cognitive products and processes.

A first, necessary step to demonstrate support for these and other potential scar processes is that cognitive products

and processes worsen after experience of psychopathology. Research that examined the cognitive scarring after various forms of psychopathology has been mixed. Consistent with a cognitive scar model, deficits in EF, memory and attention remain in individuals in remission (e.g., euthymic BD, remitted depression, see Cognitive Processes). Findings for cognitive products, such as negative attributional style or rumination, have found mixed evidence for the cognitive scar hypothesis (e.g., remitted depression and BD; see Cognitive Products). However, since this evidence largely comes from cross sectional studies, it is possible that cognitive deficits preceded illness onset, or that there is a transactional positive feedback loop between cognitive deficits and psychopathology. Answering these questions will require more prospective longitudinal studies, starting before disorder onset and following individuals over the course of their illness and into remission.

Longitudinal Measurement Invariance: Stability and Change

Investigating the degree of stability and change in cognitive influences to psychopathology is a fundamental area of inquiry in developmental psychopathology. Yet, surprisingly sparse research has examined this core issue: "the degree of stability of cognitive vulnerability from childhood to adulthood is unknown" (Rutter, Kim-Cohen, & Maughan, 2006, p. 283). Examining the degree of stability and change in cognitive risks, and the likely variance in stability estimates across key developmental periods, can vitally inform mechanisms that may help to explain the strongly chronic, recurrent nature of most forms of psychopathology after initial onset and symptom increases occurring with most child- and adolescent-onset disorders.

Examining *measurement invariance* across development is a first and necessary step when considering both stability and change in cognitive influences to psychopathology, but this is a little researched and frequently ignored topic. In essence, the core question is whether any particular cognitive product or process, at the latent construct level, is the same when assessed with available measures across development. For example, multiple measures exist to assess individuals' negative cognitive style for different ages: young children (Conley et al., 2001), older children (Mezulis et al., 2006), adolescents (Hankin & Abramson, 2002), and adults (Haeffel et al., 2008). It is generally assumed that each of these manifest measures is assessing the latent construct of a negative cognitive style, and the evidence that each of these measures predicts later depressive symptoms, as the theory postulates, is presumed and taken as prima facie evidence to demonstrate that the manifest measures are, indeed, assessing the same core latent construct. However, virtually no research has been conducted to rigorously and properly examine whether the extant manifest measures used presently by investigators are, in fact, assessing the same latent construct over different developmental periods (i.e., measurement invariance; Widaman, Ferrer, & Conger, 2010).

Equivalently, using the same manifest measure across different developmental periods (e.g., childhood through adolescence and adulthood) still necessitates examination of measurement invariance; utilization of the same measure cannot be assumed to assess the same latent construct across development. Establishing that a particular measure, at the manifest level, is assessing the same theoretical construct and process at the latent level, is a fundamental step. Yet this critically essential work has not been conducted, so research investigating vital developmental psychopathology questions of cognitive influences, including stability, change, and developmental origins, rest on the untested assumption that presently used manifest measures of cognitive products and processes demonstrate a reasonable degree of measurement equivalence over time and across development.

Measurement invariance issues also connect to and raise questions concerning homotypic and heterotypic continuity. For example, is rumination exactly equivalent (homotypic continuity), at both the observed measurement and at the conceptually defined process level, across development (e.g., ages 5, 8, 13, 16, 25, 40, 68), or is rumination similar at the latent process level (e.g., perseverating on negative mood), albeit with some change in its manifestation and form (i.e., heterotypic continuity)? Relatedly, trying to establish the degree of continuity, especially whether the particular cognitive product and process conforms best to homotypic or heterotypic continuity, is further complicated by a lack of established theory and empirical knowledge on the overall hierarchical structure and taxonomy that organizes and connects the different cognitive products and processes together. How does this architecture and structure change across development (e.g., consolidation of cognitive influences) and as a function of psychopathology (e.g., consequence effects)? Issues of structure and consolidation are discussed in greater detail later in the next section, but it's important to highlight here that homotypic and heterotypic continuity concerns directly relate to issues of structure and consolidation across development.

Assuming that observable methods to assess cognitive influences exhibit reasonable measurement invariance, then processes underlying the degree of stability and change in these cognitive risks can be examined. A useful and

rigorous approach to understanding processes in stability and change derives from conceptual and empirical advances in research on basic personality development (Caspi, Roberts, & Shiner, 2005; Fraley & Roberts, 2005), including examination of rank-order stability and mean-level changes over time. Different processes, including (1) a trait-like model, (2) a contextual/autoregressive model, and (3) a combined trait/contextual model, can explain how cognitive risks maintain rank-order, or test–retest, stability over time. Trait models predict that the empirically obtained test–retest correlations will be invariant as the period between test–retest interval increases because there is a stable, enduring force (i.e., the trait cognitive risk) that organizes the manifestation of measured cognitive risks over time. In contrast, contextual models predict that the magnitude of the test–retest correlations for cognitive risk will decrease monotonically as the length of the test–retest interval increases (i.e., an autoregressive simplex pattern; Kenny & Zautra, 2001) because there is no enduring influence that drives the stability over time.

Testing which process (i.e., trait, autoregressive, combination) may best account for the degree of stability in cognitive risk over time requires that multiple waves of data be used. The two-time point study most typically used to demonstrate test–retest reliability is inadequate for formally and rigorously investigating the processes underlying the degree of stability observed over those two time points, regardless of the length of time (Fraley & Roberts, 2005), because it is the pattern of test–retest correlations over time, not the strength of the test–retest correlation, that indicates whether the particular cognitive influence is understood to be organized best from a trait, contextual, or a combined process. With multiple assessments of longitudinal data, the pattern of test–retest correlations can be examined to evaluate whether a trait-like or autoregressive contextual model best explains the rank-order stability of data over time. Moreover, longitudinal analyses can determine the mean levels of stability over time for the participants on average.

To date, little research has examined the degree of stability and change, and the underlying processes that give rise to that stability, in cognitive risks to psychopathology. The first examination of the processes underlying stability of cognitive vulnerability, in any age group, used a diary design with late adolescents who completed daily ratings of the cognitive inferences they made for the most negative event experienced every day for a month (Hankin, Fraley, & Abela, 2005). Findings showed mean-level stability: negative inference scores did not change on average over 35 days. Moreover, moderately stable rank-order stability was observed, and importantly, an enduring, trait-like model best explained the pattern of test–retest stability. Building on this approach and investigating additional cognitive products in younger adolescents (ages 11–16; sixth to tenth grades), Hankin (2008b) examined the degree of stability and change in negative cognitive style, dysfunctional attitudes, and rumination across four time points. A negative cognitive style demonstrated mean-level stability, whereas rumination and dysfunctional attitudes showed some mean-level change. The magnitudes of test–retest reliabilities were moderately high for a negative cognitive style (mean $r = .52$), and more modest for rumination (mean $r =. 28$), and dysfunctional attitudes (mean $r = .26$). The pattern of these test–retest reliabilities over time was best explained by relatively trait-like enduring processes for a negative cognitive style and dysfunctional attitudes, whereas both enduring and contextual dynamics contributed to the moderate stability for rumination. Future research is needed to continue this line of work to younger ages to better establish when these cognitive products begin to coalesce into the enduring, relatively trait-like risks to psychopathology and to expand this approach to understanding the dynamics underlying stability and change to other cognitive products and processes across various developmentally salient age groups.

Taken together, these findings showing that a negative cognitive style, in particular, already demonstrates modestly strong stability, and that enduring dynamic forces underlie this stability, have interesting applications when synthesized with established developmental epidemiological facts. It is intriguing that a negative cognitive style is already relatively trait-like by age 11 when the modal increase in depression rates occurs later in adolescence (especially ages 15–18; Hankin et al., 1998). Moreover, these findings open new questions that convey interesting translational implications for the timing of delivering evidence-based efforts to reduce depression rates. Would it be more effective to implement cognitive-behavioral (CB) depression preventions (Brunwasser, Gillham, & Kim, 2009) before certain cognitive risks, such as a negative cognitive style, have crystallized into relatively trait-like vulnerabilities to depression (i.e., before age 11)? How long do the effects of CB-based preventions last in changing these cognitive vulnerabilities that are believed to be important mechanisms of change in the prevention of depression? Meta-analytic reviews of depression prevention trials indicate that effects are generally short-lived (Horowitz & Garber, 2006; Stice, Shaw, Bohon, Marti, & Rohde, 2009), and similarly, research on CB treatments

of depression and anxiety reveals these psychotherapies exhibit enduring effects (e.g., relatively improved effects lasting up to 5 years), although the psychoactive mediating mechanisms appear to be mainly palliative and do not endure (Hollon, Stewart, & Strunk, 2006). As such, would reductions in core cognitive risks, if changed in late childhood, persist over several years to meaningfully decrease the surge in depression rates that are most likely to occur with modal age of onset in later adolescence?

Escaping the Silos: Building Integrative Models Across Boundaries

Taxonomy and Stucture of Cognitive Risks: Informing Consolidation in the Interrelation Among Cognitive Risks

As alluded to earlier, there exists no theoretically specified nor empirically determined structure of either cognitive products or processes, separately, nor both cognitive influences together in a hierarchical taxonomy model. The main issue is that numerous cognitive products, in particular, have been postulated and investigated as putative risks to psychopathology. Yet little is known about how these different cognitive products (each of which carries a different name and derives from supposedly relatively unique theoretical underpinnings), relate to each other, and how much they overlap. In other words, do cognitive products demonstrate factorial independence—with other cognitive products as well as possibly conceptually similar individual differences (e.g., neuroticism, as a personality trait, that shares some conceptual and empirical overlap with several cognitive products)?

In contrast and as a shining example of what is needed, considerable research, both theoretical and empirical, has reasonably well established the structure of temperament (e.g., Rothbart & Bates, 2006) and personality traits (e.g., Caspi et al., 2005). A consequence of a well-established personality taxonomy is that existing traits, as well as potentially new ones, can be placed systematically, organized, and understood conceptually within the larger trait taxonomy and structure. Moreover, a fair amount of work has investigated questions of personality development, including stability and change in traits (e.g., Roberts & DelVecchio, 2000) as well as developmental changes in structure and underlying processes contributing to the degree of stability (e.g., Fraley & Roberts, 2005) of these traits over time.

However, the essential theoretical and empirical work has not been conducted on the hierarchical structure of many of the cognitive influences that are the focus of this chapter. This is another concrete example of the general silo approach in much of the scientific inquiry that has taken place with cognitive influences to psychopathology. The factor structure of many cognitive processes has been well defined, at least in healthy individuals (e.g., see Executive Function for a review of the factor structure of EF component processes). However, only a handful of factor analytic studies have examined the factor structure of cognitive products. Those done with young adult samples (e.g., Hankin, Lakdawalla, Carter, Abela, & Adams, 2007) show that each of the cognitive risks (e.g., negative cognitive style, dysfunctional attitudes, rumination) are moderately correlated with each other but factorially independent (i.e., not completely overlapping at the latent level) and are mostly separate from related, but noncognitive, constructs (e.g., low self-esteem, neuroticism, depressed mood). Factor analytic studies of youth are more mixed but tend to suggest that some of these cognitive products overlap and are less distinct at younger ages (e.g., Adams, Abela, & Hankin, 2007). To our knowledge, no other research has examined the factorial structure and latent taxonomy of other cognitive products.

While it is a clear priority to establish a hierarchical structure of both cognitive products and processes to psychopathology across developmental periods, another important, yet under investigated, area is evaluating how the various cognitive risks interrelate with one another and potentially become more consolidated over time. Examining the interrelation among different risks is important because the various forms of cognitive products, for example, may all emerge and stabilize along a similar time-course, but each of these cognitive risks may be relatively independent of each other earlier in development and then begin to become increasingly more interrelated and coalesce. Indeed, this pattern of increasing interrelatedness would be expected based on research in the temperament and personality development literatures (e.g., Caspi et al., 2005), in which many more narrow, lower-order factors are observed early in development, but by middle adolescence and throughout adulthood, the standard personality taxonomy (e.g., Big-5 factors) is routinely obtained. The results from the few factor analytic studies of depressogenic cognitive products suggest that these cognitive risks are more distinct in children than in adolescents and young adults (Hankin et al., 2007). It appears that the various cognitive risks may initially be relatively independent of one another but then become increasingly more interrelated during the transition from childhood to adolescence. As multiple cognitive products potentially coalesce into a consolidated *set* of moderately intercorrelated cognitive risk, youths' degree of vulnerability to psychopathology may

potentiate. An interesting hypothesis in need of empirical examination is that this contamination and consolidation process may occur around the same time that prior researchers (Nolen-Hoeksema et al., 1992; Turner & Cole, 1994) earlier hypothesized that some cognitive risks first emerge.

Given that cognitive risks appear to become more interrelated with one another with progressing age, different approaches toward conceptualizing the relationship among multiple cognitive risks may be optimal for youth at different developmental stages. When youths' cognitive risks are still relatively distinct, knowledge of any particular factor may convey minimal information about overall degree of vulnerability to psychopathology, so a weakest link approach may be the most appropriate conceptualization at this stage: The child's strongest cognitive risk factor may likely be the best indicator of his or her propensity to engage in negative thinking leading to psychopathology. As cognitive risks become more interrelated with one another over time, however, knowledge of a child's level with respect to any given factor provides information about his or her levels with respect to other cognitive risks. At this point in development, an additive or multiplicative model may become more appropriate than a weakest link approach as the presence of multiple vulnerabilities may become an equally, if not more, important indicator of the likelihood the individual engages in negative thought processes contributing to psychopathology (see Abela & Hankin, 2008 for expanded discussion of the strengths and weaknesses of each of these models).

It is axiomatic in developmental psychopathology that there exist multiple developmental pathways (equifinality) and that the various influences leading to these pathways cut across multiple levels of analysis (e.g., from genes to neural circuits to behaviors and cognitions in relevant social contexts in an ecological framework). Given that multiple factors and processes are needed to predict known heterogeneity in causes for prevalent psychopathologies, it is essential to formally organize and consider how the various risk and resilience factors and mechanisms are structured together (i.e., a weakest link, additive, or multiplicative approach), when across development each of these model approaches provides the best fit for organizing cognitive risks, and how these best predict psychopathologies and for whom.

Links Between Cognitive Processes and Products: Still a Bridge Too Far?

In addition to determining the structure within cognitive products and processes, a further challenge is to determine how cognitive products are related to cognitive processes. Cognitive products, such as attributions, biases, and ruminative thoughts must necessarily arise from basic cognitive processes. However, efforts to understand how cognitive processes and products are linked are still in their infancy, akin to the early years of cognitive neuroscience, when scientists knew that neural events must give rise to cognitive processes but had very little idea of how they did so. Just as cognitive neuroscience has made great strides in discovering links between brain and cognitive processes over the past 20 years, the field seems poised to make significant progress in linking cognitive processes and products in coming years.

Indeed, in a few areas progress is already being made toward this goal. For example, two closely related models have recently been proposed, linking EF deficits to cognitive products in depression (Joormann, Levens, & Gotlib, 2011; Joormann, 2010b; Koster, De Lissnyder, Derakshan, & De Raedt, 2011), and aspects of these models have been empirically supported (e.g., Berman et al., 2010; Joormann & Gotlib, 2008; Zetsche, Avanzato, & Joormann, 2012). Specifically, according to these models, the experience of a negative event triggers negative mood and cognitions, which are normally transient, with mood-congruent cognitions quickly being replaced by more positive thoughts that regulate and repair the negative mood. However, depression is associated with deficits in EF, which lead to difficulty shifting attention and updating the contents of working memory to remove negative material and replace it with the more positive material that would normally aid in mood repair. As a result, negative material remains in working memory, leading to increased rumination, decreased reappraisal and impaired problem solving, which in turn reinforce and maintain the negative mood and activate negative cognitions (Joormann et al., 2011; Joormann, 2010b; Koster et al., 2011).

In other areas, there has been speculation regarding how cognitive products and processes may be linked. For example, there are potential parallels between hostile attributional bias and attentional bias toward negative information. However, research on these topics is still nascent, and efforts to understand the mechanisms giving rise to cognitive products are likely to face some significant challenges distinct from those faced by efforts to map cognitive processes onto neural mechanisms. In particular, many cognitive processes rely on brain networks that, while complex, are fairly well defined (e.g., the medial temporal lobe memory system and the frontal-parietal-striatal EF network). Identifying the brain networks involved then provides traction for understanding the component

mechanisms (e.g., unique properties of the hippocampus that support memory). However, cognitive products seem highly unlikely to arise from dedicated brain networks (e.g., there is not likely to be an attribution network). Rather, cognitive products are most likely emergent phenomena of multiple interacting cognitive processes, supported by widely distributed neural activity, making it difficult to gain traction in understanding the mechanisms involved.

How Do We Get There from Here? Bridging Multiple Levels of Analysis

The research reviewed in this chapter spans many levels of analysis, from probing people's accessible thoughts and behaviors through self-report, to assessing their behavioral performance on laboratory tasks, to measuring specific aspects of brain structure and function, and finally connecting these to psychopathological phenotypes. Furthermore, within each of these levels of analysis, there are myriad methodological approaches. Each level of analysis provides valuable information, and each methodological approach has its own strengths and weaknesses. Certainly, there is no one right approach. Rather, like the parable of the blind men and the elephant, each approach provides only partial information, which when taken alone can be misleading.

To give just one example, fMRI provides valuable information about which areas of the brain may be functioning differently in individuals with psychopathology. However, there are limitations to what fMRI can tell us about *how* those brain areas are functioning differently. For example, fMRI signal reflects a mixture of excitatory (e.g., glutamatergic) and inhibitory (e.g., GABAergic) neural activity, with the contributions of each depending on the task, the brain region, and many unknown variables (e.g., Logothetis, 2008). Thus, reduced fMRI signal (hypoactivation) can be the result of reduced activity of excitatory neurons, inhibitory interneurons, or both—the specific neural mechanism underlying the observed change in brain activation cannot be determined by fMRI alone. Thus, while correlational mapping of fMRI brain activation and psychopathology has made important contributions, it must be combined with other methods to move beyond the *where* and *how much activation* questions it can address to specific mechanistic *how* questions it cannot (e.g., Munakata, Chatham, & Snyder, 2012b).

Likewise, deficits on behavioral tasks or differences on self-report measures may arise from a mixture of sources (e.g., deficits in different cognitive processes or use of different strategies may contribute to poor performance on a task, and responses to questions about cognitive products may arise from different streams of biased information processing). Thus, to build more complete cognitive models of developmental psychopathology that can address *how* questions, to construct a picture of the whole elephant as it were, it will be necessary to combine evidence across multiple methods and levels of analysis.

Areas in which progress in generating such integrated models has been made include linking EF deficits in schizophrenia to specific abnormalities in the dopamine system (Barch & Ceaser, 2012), attention biases in depression to specific abnormalities in the serotonin system (Gibb et al., 2013), and connecting cognitive risks to multiple levels of analysis spanning genetics, neurobiology, and physiology (e.g., Hankin, 2012).

An example of an area in which multiple levels of analysis are just beginning to be linked is executive function deficits associated with depression. Here, a more detailed model is slowly emerging that has combined findings across disparate disciplines and methods. People with depression report difficulties with concentration and completing goals (symptom level); behavioral testing indicates deficits on a wide range of EF tasks, suggesting a problem with processes common to all EF tasks, such as maintaining goals in working memory (behavioral level; Snyder, 2013) neuroimaging research finds that individuals with depression have less activation in prefrontal brain areas involved in working memory (neural networks level; e.g., Fitzgerald, Laird, Maller, & Daskalakis, 2008); spectroscopy studies suggest that these lower levels of activation may be due to reduced glutamatergic function (neurotransmitter level; e.g., Yüksel & Ongur, 2010); and finally, computational computer simulations and neural recordings in animals suggest that working memory in prefrontal cortex depends on sustained neural firing triggered by glutamatergic signaling (cellular level; e.g., O'Reilly, Hazy, & Herd, 2013).

Fitting these pieces of evidence together across levels of analysis can generate a hypothesized model—concentration difficulties associated with depression are due to reduced prefrontal glutamatergic functioning leading to impaired ability to maintain goals in working memory through sustained neural firing. This model may prove to be wrong, but it has the virtue of generating specific, testable predictions (e.g., the largest impairments should be found on tasks that most heavily tap active goal maintenance) and implications for treatment (e.g., glutamatergic drugs should improve EF and concentration in individuals with depression; see, e.g., (Hashimoto, 2009) for promising research on novel glutamatergic antidepressants). However, such multilevel integrative models are still relatively rare, and to our knowledge no model has thus far spanned

from cognitive products to specific neural mechanisms. Building such models will undoubtedly be challenging, and will require a major interdisciplinary effort, but we believe they have tremendous potential for understanding the mechanisms involved in the cognitive aspects of psychopathology at a level that will enable the generation of new developmental clinical scientific knowledge and translation to new treatment and prevention approaches.

Transdiagnostic Approaches: Bridging Multiple Forms of Psychopathology

One theoretical approach that has received increasing attention is the study of common processes across seemingly separable constructs. This is known as a *transdiagnostic* approach to examining risk for psychopathology (e.g., McLaughlin & Nolen-Hoeksema, 2011). Our review of cognitive products and processes in relation to multiple prevalent psychopathologies suggests that certain cognitive risks may broadly predict several forms of emotional and behavioral disorders. Here we comment on two issues to consider that require additional future research with respect to a transdiagnostic approach to cognition and development of psychopathology.

The transdiagnostic approach to studying cognitive constructs, in particular, can be illustrated by an examination of rumination, worry, and postevent processing, which are three cognitive constructs hypothesized to fall under the common process of repetitive negative thinking (RNT). It is thought that these three cognitive constructs are similar in that they all involve a repetitive thought process; however they are distinguishable across different forms of psychopathology by their content. Rumination is commonly linked to depression, worry to generalized anxiety disorder, and post-event processing to social phobia (see McEvoy, Mahoney, & Moulds, 2010 for review). For example, in an effort to disentangle the common and unique components of these three cognitive constructs, McEvoy and colleagues (2010) factor analyzed common measures of RNT, including worry, rumination, and post-event processing, and they identified a common RNT factor. This common RNT scale was associated with symptoms of depression, anxiety, general distress, anger, and shame. This study demonstrates that putatively different cognitive products may be more appropriately and parsimoniously conceptualized as a single common process of repetitive negative thinking across various types of psychopathology and emotional states.

On the other hand, cognitive factors that appear transdiagnostic at one level of analysis may not be when more detailed measures at multiple levels of analysis are considered. Just as many problems with a car (e.g., a dead battery, broken starter, or being out of gas) could all lead to the same outcome (the car won't start), the same cognitive endpoint might be reached by many different underlying mechanisms (*equifinality*). For example, at the level of performance on neuropsychological tasks, EF deficits appear to be a transdiagnostic feature of psychopathology. However, as we reviewed, in some cases these shared behavioral deficits may arise from distinct neural mechanisms (e.g., perturbations in different neurotransmitter systems). Thus, determining whether a product or process is truly transdiagnostic requires escaping both diagnostic and methodological silos to consider underlying mechanisms at multiple levels of analysis.

One area where progress has been made in doing so is EF. Here, we discuss in some detail efforts to understand why transdiagnostic impairments in EF occur, as an example of how interdisciplinary research can shed light on transdiagnostic processes more broadly. What gives rise to broad patterns of impairment in core EF processes across most disorders? First, these deficits cannot be easily explained by nonspecific factors such as psychomotor slowing, differences in IQ or education, or medication use (Barch, 2005; Forbes et al., 2009; Snyder et al., 2015; Snyder, 2013). Second, in most cases, effect sizes are similar across the core EF domains, suggesting that psychopathology may be associated with impairment in what is common across EF tasks (common EF, posited to be monitoring for and maintenance of task goals and contextual information; (Miyake & Friedman, 2012), rather than a specific aspect of EF. Future research is needed to refine understanding of how such broad EF deficits arise. One possibility is that impaired function in brain networks involved in EF, including PFC, may lead to broad impairment in EF.

Indeed, extensive neuroimaging evidence indicates that individuals with many forms of psychopathology have structural and functional abnormalities in brain networks involved in EF. Meta-analyses have demonstrated reduced prefrontal grey and/or white matter in individuals with schizophrenia (e.g., Yu et al., 2010), BD (Yu et al., 2010), depression (Liao et al., 2013; Bora, Fornito, Pantelis, & Yucel, 2012), OCD (Menzies et al., 2008), and ADHD (van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). Alterations in prefrontal activation during EF tasks are also widespread across disorders. While both decreased (hypoactivation) and increased (hyperactivation) activation relative to healthy controls have been reported, in general reduced activation is found when task performance is impaired, and increased activation is found when task performance is unimpaired, consistent with inefficient processing

(e.g., Cortese et al., 2012; Diener et al., 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Menzies et al., 2008b; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Patel, Spreng, Shin, & Girard, 2012).

Thus, multiple forms of psychopathology all appear to be associated with prefrontal structural abnormalities and functional inefficiency. However, the cellular level abnormalities underlying these broad changes in prefrontal function may vary across disorders. For example, while depression is associated with *reduced* glutamate function (e.g., Luykx et al., 2012), individuals with BD show *increased* glutamate levels in PFC (Gigante et al., 2012). The role of cellular level mechanisms in EF impairments has been most extensively investigated in individuals with schizophrenia. Phasic dopamine bursts, which normally serve to regulate updating of goals and information in working memory, are dysregulated in schizophrenia, leading to a failure to appropriately update relevant information into working memory and lack of stability of representations in the face of interference (Barch, 2005; Eisenberg & Berman, 2010). Thus, altered dopamine function is one key candidate mechanism that may underlie impaired common EF in schizophrenia, leading to impairments across all EF tasks.

In addition, PFC dysfunction may differentially impact different posterior and subcortical areas in different disorders. For example, in the case of PTSD, hypoactivity of the prefrontal–parietal EF network is hypothesized to lead to a loss of top-down control over emotion and memory systems (e.g., the amygdala and hippocampus, (Patel et al., 2012), as well as EF impairments. In addition, the largest deficit for individuals with OCD was for updating, which is believed to depend critically on striatal gating of information into prefrontal cortex (Hazy, Frank, & Reilly, 2007). This suggests that updating may be particularly impaired in people with OCD, since both striatal and prefrontal dysfunction may contribute to deficits on updating tasks. However, there have been few studies of updating in individuals with OCD, so additional research is needed to explore this possibility. Thus, while multiple disorders may be associated with prefrontal dysfunction leading to broad impairment in EF, the underlying neurobiological abnormalities, at the cellular and network level, may be quite distinct.

A further important question is how these prefrontal abnormalities, and thus EF deficits, arise. There is some evidence that PFC abnormalities and impaired EF may be endophenotypes for psychopathology. Significant, though more subtle, impairments in EF and prefrontal abnormalities have been reported in currently healthy individuals with greater genetic risk for schizophrenia (Barch, 2005), BD (Bora et al., 2009), OCD (Menzies et al., 2007) and PTSD (Gilbertson et al., 2006).

These findings suggest that EF deficits may proceed, and potentially be a risk factor for, psychopathology. Although there have been few longitudinal prospective studies which could speak to this issue, there is some evidence that EF deficits may precede illness onset. Specifically, early adolescent EF predicts adult psychosis (Cannon et al., 2006), preschool EF predicts middle-childhood ADHD (even controlling for preschool ADHD symptoms; Campbell & Stauffenberg, 2008), and pre-trauma EF predicts post-trauma PTSD (Parslow & Jorm, 2007). On the resilience side, individuals who have experienced trauma but do not have PTSD have greater PFC activity not only compared with individuals with PTSD, but also compared with healthy controls who have not experienced trauma (Patel et al., 2012). It is thus possible that individual differences in prefrontal function and resulting differences in EF predispose some people to develop psychopathology, while buffering others (Aupperle et al., 2012). These patterns are consistent with neurodevelopmental models of psychopathology, in which disorders are posited to be the behavioral outcome of aberrant neurodevelopment that begins long before the onset of clinical symptoms and is caused by a combination of genetic and environmental factors (Rappaport et al., 2012; Seidman, 2006).

Translational Implications

This section applies what is known about cognitive products and then processes in relation to the treatment and prevention of common psychopathologies. We consider some future directions that can be taken to further reduce mental health burden of individuals across the life span based on theoretical and empirical knowledge covered in this chapter.

Since the initial, groundbreaking clinical work of Beck (1967) and Ellis (1957), cognitive (and cognitive-behavioral, CB) therapies have been developed and rigorously evaluated for many prevalent psychopathologies. While there are important, subtle differences in these CB interventions for different disorders, all of these evidence-based interventions share an emphasis on cognitive products and processes as essential mechanisms that are hypothesized to produce meaningful symptom, emotion, and behavior change. Indeed, perusal of empirically supported treatments (e.g., see Barlow, 2008) for adults (e.g., Division 12 of APA) and youth (e.g., Division 53 of APA) reveals that CB-based interventions are established for depression, general child anxiety, Panic Disorder, PTSD, GAD, SAD,

substance abuse and dependence, binge eating disorder, bulimia nervosa, and disruptive behavioral problems. Other CB-based treatments have shown promise for other disorders, including schizophrenia (Tarrier, 2005) and BD (Miklowitz, 2008). In addition to treatments for diagnosed psychopathologies, several CB-based preventions have been demonstrated to reduce likelihood of future increases in symptoms of and episodes for depression (Horowitz & Garber, 2006; Stice, Rohde, Gau, & Wade, 2010), anxiety (Fisak, Richard, & Mann, 2011), disruptive behavioral problems (Powell et al., 2011), and comorbid internalizing and externalizing problems (e.g., Weiss, Harris, Catron, & Han, 2003).

Cognitive Products as Mediating Mechanisms and Moderators in CB-based Interventions

In addition to CB-approaches as evidence-based interventions to treat and prevent psychopathology, research has also examined various cognitive risks as mediating mechanisms of intervention effects. Despite the central importance of cognitive products and processes as putative mediators of change in CB-approaches, it is surprising that relatively few studies have empirically examined cognitive influences as mechanisms (Hundt et al., 2013 with adults; Webb, Auerbach, & Derubeis, 2012 with youth). It is worth noting that this relative paucity of cognitive mediation research is not unique to investigation in CB-based interventions, but rather applies broadly to general lack of understanding of how and why psychotherapy is efficacious and leads to change (e.g., Kazdin, 2009). Such research on mediating mechanisms is important also because it can provide evidence regarding cognitive risks as a possible causal risk factor in developmental psychopathology (Kazdin et al., 1997; Kraemer et al., 2001).

Much of the research on cognitive mechanisms of change in psychotherapy has focused on depression (e.g., Kazdin, 2007), and most of that has used adult samples (see Garratt, Ingram, Rand, & Sawalani, 2007 for review). As such, the following studies reflect this knowledge base to provide the most evidence-based examples of how cognition may explain how psychotherapies work. Generally a number of studies have shown that CBT for depression in adults (Garratt et al., 2007) and adolescents (Weersing, Rozenman, & Gonzalez, 2009) is related to reductions in cognitive products, but not all have formally examined mediation to link change in negative cognitions to subsequent change in symptoms. Among youth, CBT for anxiety produced moderate to large effects in various theoretically specified mechanisms, whereas CBT for depression yielded small effects for change (Chu & Harrison, 2007).

Some individual studies suggest that particular cognitive risks may mediate CB-based intervention effects. A negative attributional style has been shown to mediate the efficacy of CBT for depression (e.g., Barber & DeRubeis, 2001). Dysfunctional attitudes (or automatic thoughts, depending on the study) mediated effects of CBT for adult depression (e.g., Beevers, Keitner, Ryan, & Miller, 2003; Warmerdam, van Straten, Jongsma, Twisk, & Cuijpers, 2010) and adolescent depression (e.g., Jacobs et al., 2009). Moreover, mediation through dysfunctional attitudes has been shown in CBT for adult alcoholism comorbid with depressive symptoms (Ramsey, Brown, Stuart, Burgess, & Miller, 2002), and preliminary mediation of effects for CBT were found in an open trial for schizophrenia (Morrison et al., 2012). There have been demonstrations of specific mediation for dysfunctional attitudes in CBT versus interpersonal psychotherapy for adult depression (Quilty, McBride, & Bagby, 2008) and versus pharmacotherapy (Dozois et al., 2009; Garratt et al., 2007). Indeed, the preponderance of data suggest that antidepressants modify many of the cognitive biases in depression (e.g., Roiser, Elliott, & Sahakian, 2012). Moreover, several brain areas and cognitively mediated neural circuits implicated in depression etiology show change resulting from CBT as well as pharmacotherapy (Roiser et al., 2012). Anxiety schema change (Teachman, Marker, & Smith-Janik, 2008) and panic appraisals (Cho, Smits, Powers, & Telch, 2006) in Panic Disorder mediated effects of CBT for panic. Dysfunctional trauma-related appraisals demonstrated temporal precedence in mediation for Trauma-Focused CBT in treatment for PTSD (Kleim et al., 2012). Self-efficacy beliefs mediated efficacy in CBT, specifically in contrast to IPT, for bulimia among adults (Wilson, Fairburn, Agras, Walsh, & Kraemer, 2002).

Regarding rumination as a putative mechanism, research has shown that reductions in rumination mediated effects in mindfulness based CBT for adult depression (Van Aalderen et al., 2012). It has been suggested that addressing repetitive negative thinking, broadly defined, represents an efficient way to target the cognitive risk and maintenance factors that are transdiagnostically present across multiple psychopathologies (McLaughlin & Nolen-Hoeksema, 2011). Mindfulness-based interventions, in which clients are taught to emotionally disengage from recurrent negative thoughts (e.g., rumination) instead of letting them adversely affect one's mood, may be another therapeutic approach to reducing repetitive negative thinking and psychopathology (Rood et al., 2010).

While this review is consistent with the view that cognitive products mediate effects of CB-based interventions,

it is noteworthy that few studies have rigorously examined essential mechanism questions and have properly examined mediation (Kazdin, 2009). Most study designs do not go beyond showing that CBT is associated with reductions in cognitive products and symptoms and that these two variables are correlated, so the temporal precedence in the vast majority of cognitive mechanism studies of therapy is unknown. Indeed, results from a CB-based prevention trial of adolescents at-risk for depression highlight that cognitive risks may be changed by the intervention, but the temporal precedence of change in cognition prior to change in symptoms is not guaranteed (Stice et al., 2010) and still needs to be established.

In addition to examination of mediation, a few studies have investigated whether cognitive products moderate treatment outcome in depression. In a review of adult CBT for depression studies, dysfunctional attitudes were reported to moderate CBT response (Hamilton & Dobson, 2002). The available studies with depressed adolescents suggest likewise. Cognitive distortion predicted depression in treatment (Brent et al., 1998). High cognitive distortions helped depressed adolescents receiving combined pharmacotherapy and CBT (Curry et al., 2006), although dysfunctional attitudes did not predict adolescent treatment response across intervention modalities in contrast to the adult research (Jacobs et al., 2010).

Cognitive Products as Mediators and Moderators in Prevention Work

With respect to preventive interventions, selective and indicated programs, such as those focused on youth with enhanced cognitive risk (e.g., negative cognitive style), have been demonstrated to be more effective than universal preventions for youth depression (Horowitz & Garber, 2006), although definitive tests of moderation have not been examined (Garber, Korelitz, & Samanez-Larkin, 2012). A negative cognitive style partially mediated the effects of a CB-based prevention, the Penn Resiliency Program, on depressive symptoms (Brunwasser et al., 2009).

Cognitive Processes as Mediators in Interventions

Regarding translation implications for the cognitive processes that comprised the focus of this chapter, pretreatment cognition has been shown to predict treatment response. In particular, EF and episodic memory task performance predict pharmacotherapy response in individuals with depression (McLennan & Mathias, 2010), schizophrenia (Kim et al., 2008), OCD (e.g., D'Alcante et al., 2012), and BD (e.g., Gruber, Rosso, & Yurgelun-Todd, 2008). Although the precise reasons are unclear (e.g., there could be neurobiological explanations), poor medication compliance is the most likely and parsimonious explanation because these findings hold across several different types of psychiatric medications. Moreover, over-general autobiographical memory predicts poor clinical outcomes after treatment, over and above what is predicted by initial symptoms (Sumner et al., 2010). Finally, Cognitive Bias Modification training, which redirects attentional biases from negative emotional stimuli (e.g., threat) to more neutral stimuli, has been shown to reduce symptoms of anxiety and depression (e.g., see MacLeod & Mathews, 2012 for review). Redirecting subtle perceptual cognitive biases in emotion recognition toward happy faces, and away from angry faces, can reduce anger and aggression, consistent with Dodge's model via mediating hostile attribution bias (Penton-Voak et al., 2013). It is important to note that despite these individual studies finding positive, preliminary evidence, to date none of these interventions focused on changing cognitive processes has been established as fully evidence-based according to rigorous EST criteria (e.g., Chambless & Hollon, 1998).

In addition to cognitive processes predicting later treatment response, the opposite direction, in which interventions affect cognitive processes, has also been investigated. The majority, but not all, studies find that stimulant medications improve cognitive performance in individuals with ADHD, and more studies have found positive effects on EF and attention than memory (see Pietrzak, Mollica, Maruff, & Snyder, 2006 for review). Cognitive rehabilitation interventions, which are aimed at teaching compensatory strategies (e.g., use of lists and memory cues, dividing tasks into smaller steps, etc.), can improve functional outcomes (e.g., occupational/academic functioning) in individuals with schizophrenia (e.g., see Kluwe-Schiavon, Sanvicente-Vieira, Kristensen, & Grassi-Oliveira, 2013 for review), BD (e.g., Deckersbach et al., 2010), and ADHD (e.g., Hahn-Markowitz, Manor, & Maeir, 2011). There is less research on cognitive remediation in individuals with depression or anxiety disorders, although it is interesting that some therapies (e.g., behavioral activation; e.g., Dimidjian, Barrera, Martell, Muñoz, & Lewinsohn, 2011) incorporate compensatory strategies (e.g., memory cues to engage in an activity, like putting walking shoes by the door). There are interesting suggestions that certain medications (e.g., Modafinil, a cognitive enhancer) have potential for improving EF in individuals with depression (e.g., improved response to antidepressant treatment with Modafinil (Abolfazli et al., 2011), but these effects are not yet well established with cognitive

control (Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011).

Finally, it is notable that there is less evidence in support of direct training of cognitive processes (i.e., targeting the weakness rather than compensatory strategies). In general, while task performance improves, there is little evidence that training effects generalize to real-world function or improve clinical symptoms (e.g., Rabipour & Raz, 2012). Two possible exceptions are Cognitive Bias Modification, as reviewed earlier, and EF training in children with ADHD, which may decrease symptoms and increase academic function (Rabipour & Raz, 2012). However, a recent meta-analysis found evidence for only very small and nonsignificant effects EF and attention training programs on academic performance and blinded subjective ratings of children with ADHD, although there were very small but significant improvements on nontrained cognitive tasks (Rapport, Orban, Kofler, & Friedman, 2013). It is not clear to what extent these findings reflect genuine limitations of cognitive training in general, versus problems with the specific training programs (many of them commercial products); for example, many of the programs focus on training the least impaired aspect of EF in children with ADHD, simple working memory maintenance (Rapport et al., 2013). This leaves open the possibility that types of training that better target areas of weakness might provide better transfer. Intriguing findings suggest that certain types of EF training may change the underlying neural mechanisms to be more efficient rather than changing strategy use only (Owens, Koster, & Derakshan, 2013), suggesting that such training might transfer more broadly to processes involving the same neural mechanisms, although this has not yet been tested.

Future of Translational Directions for Cognitive Risk Research in Developmental Psychopathology

We focus on five future directions for translation of the basic theoretical and empirical work on cognitive influence into enhancement of current therapies as well as development and testing of novel intervention approaches. First, there are considerable promise and gains to be made by applying developmentally sensitive knowledge about cognitive products and processes to the personalization of treatments and preventions (Insel, 2009), especially to answer the questions of what works for whom (i.e., moderation) and why (i.e., mediation), and for which forms of psychopathology (i.e., transdiagnostically across several disorders or specifically to one). Second, novel areas for investigation include the optimal timing of when it may be best to implement evidence-based preventions to forestall the development of psychopathology, based on accumulating knowledge of the emergence, stabilization, and consolidation of cognitive influences (as discussed earlier) and for how long interventions can reduce cognitive risks in an enduring manner (whether for relapse prevention in treatments or for onset reduction via preventions). Third, a continued emphasis on investigating mediating mechanisms that underlie demonstrated efficacy of treatments is a must. While CB-based approaches are all grounded in the underlying theory of change that underscores identification and reduction of negative cognitions, which, in turn, are hypothesized to ameliorate symptoms and problematic behaviors, this does not have to be the case (Stice et al., 2010).

Also, the fundamental processes at play may change across development. In particular, incorporating capitalization versus compensation approaches to therapy change (Cheavens, Strunk, Lazarus, & Goldstein, 2012) can be an important, but relatively under-investigated, individualized approach to understanding how changes in cognition may lead to improved mental health. For example, it is not clear whether various therapies are reducing cognitive risks (e.g., dysfunctional attitudes), enhancing cognitive strengths (e.g., improved EF), or both. Fourth, this review revealed a paucity of research focusing on cognitive influences as potential moderators of treatments, especially, and preventions more formally. There likely are individual differences in cognitive products and processes that moderate intervention efficacy, and this knowledge would be very helpful for adapting and enhancing personalized treatment approaches. For example, the efficacy of CBT is believed to partly depend on individuals' EF ability, yet only one pilot study has examined this theory-based moderating hypothesis: older adults with poor EF did not respond as well to CBT for anxiety (Mohlman & Gorman, 2005). Last, tailoring interventions to make them more developmentally appropriate, based on the cognitive skills, strengths and weaknesses, as informed by the basic knowledge reviewed in this chapter, may improve efficacy when CB-interventions are designed, tested, and delivered at a level commensurate with the individual's cognitive abilities (both products and processes).

Conclusions

In closing, this chapter is the first to have reviewed several of the most prominent cognitive products and processes in relation to the development of multiple common, prevalent psychopathologies. There is a considerable corpus of evidence using cross sectional designs, predominantly

with adult samples, demonstrating that both products and processes are associated with several psychopathologies, although there are gaps in coverage. Studies that have spanned different developmental periods, from childhood into adolescence and adulthood, suggest that cognitive influences are related to psychopathologies across the life span, at least in the ages studied to date. In many cases, longitudinal studies indicate that cognitive factors, especially products, predict prospective elevations of psychopathological symptoms and disorder. Still, the evidence basis at this point is not sufficiently advanced to make definitive conclusions regarding which of several logical models may best account for these associations. Last, this review generally revealed a silo approach in the many studies that have examined isolated cognitive influences separately from other cognitive risks, and usually in relation to a single psychopathological outcome. We urge future research efforts to take a more interdisciplinary, integrative approach that seeks to synthesize conceptual and empirical knowledge across cognitive products and processes, with assessment and analysis of multiple forms of psychopathologies, across multiple levels of analysis using prospective longitudinal designs with carefully considered, developmentally appropriate samples. In summary, this chapter demonstrates that the field investigating cognitive risks to developmental psychopathology is a vibrant, active area that has produced numerous, impressive, and important findings that are critical for a comprehensive understanding of the development of psychopathology across the life span and possess clear translational import for enhancing many evidence-based, CB interventions. We are excited about the future of inquiry in cognitive influences in developmental psychopathology that can build upon the currently strong theoretical and empirical foundation and then rapidly, significantly propel knowledge forward.

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CHAPTER 9

Traumatic Stress From a Multilevel Developmental Psychopathology Perspective

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TRAUMATIC STRESS FROM MULTIPLE LEVELS OF ANALYSIS: AN INTRODUCTION

Society is increasingly preoccupied with and overwhelmed by traumatic stress. Whether it is school shootings, terrorist attacks, or multiple car pile-ups on the freeway, we cannot escape from its effects. The passage of time only sees an increase in the impact of traumatic stress on society. Advances in technology make it possible to learn instantly about traumatic events happening far away, that 100 years ago we may never had heard about at all. With smartphones beeping out tornado warnings and Amber alerts, and 24-hour cable news urging us to stay tuned to the latest bombing attack or hurricane, there is no place left to hide.

Our bodies are equipped with stress response systems that are better suited for the savannah than the office complex. Neurohormonal and neural circuit response systems allow us to respond quickly, run fast, or fight back with strength. In today's society, stress is more likely to come in the form of failing an exam or getting a virus on your computer than it is from an attack by a predator. Evolution, however, is naturally conservative. Our stress response systems are preserved through the generations, even if we don't need them as much as we used to, and in some cases they do more harm than good. When adaptation and coping are not able to keep the balance, the outcome can be extreme, with the development of mental disorders like posttraumatic stress disorder (PTSD) and depression.

How trauma affects the individual depends on a number of factors. Its impact depends on the developmental period when it occurred, social and environmental factors, physiology, prior history of stress, and individual psychological factors. This represents only a portion of all of the possible influences that are brought to bear. An understanding of the impact of traumatic stress thus requires a multilevel approach, inclusive of psychology, biology, genetics, social and cultural factors, spirituality, family and community, and existential questions about the meaning of being human. This chapter reviews the effects of trauma on the individual from a multilevel analysis approach.

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A RANGE OF PSYCHOPATHOLOGIES FOLLOWING EARLY TRAUMA: TRAUMA-SPECTRUM DISORDERS AND THE MULTILEVEL APPROACH TO THE ASSESSMENT OF THE TRAUMA RESPONSE

Bremner argued for a concept of *trauma-spectrum disorders* (Bremner, 1999, 2002a), as a group of mental disorders that all have their links in trauma, usually occurring in childhood. These disorders include PTSD, some cases of depression related to early trauma or abuse, dissociative identify disorder (DID), and borderline personality disorder (BPD). The model also acknowledges that substance abuse, psychosomatic disorders, and the increased risk for disorders like heart disease are part of the spectrum of outcomes related to psychological trauma. As such the model permits an assessment of the full range of effects on trauma on the individual, and is not limited by, for example, an emphasis on a single psychiatric disorder as defined by specific criteria as outlined in sources such as the Diagnostic and Statistical Manual (APA, 2000).

The trauma spectrum model illustrates the principle of multifinality, in which one cause leads to multiple outcomes (Cicchetti & Rogosch, 1996). For instance, DID is characterized by alterations and distortions in personal identity, and is associated with symptoms of depersonalization (feeling out of body), derealization (feeling like you are in a dream) and amnesia (gaps in memory). BPD involves intense feelings of emptiness and fears of abandonment with associated disruptive relationships and self-destruction. Both are closely linked with early trauma and are more common in women, as is depression, which in about half of patients is linked to early trauma (Zanarini, 1997). Therefore, one event can have multiple outcomes. In other words, if two individuals are exposed to the same trauma, one might develop DID, another BPD, or BID with comorbid depression. There are multiple factors that go into determining the outcomes following trauma.

The trauma-spectrum disorders model predicts that early trauma results in specific changes in brain and neurobiology that underlie the symptoms of PTSD, BPD, DID and depression in women with early childhood abuse. Additionally, PTSD is considered to be more appropriately grouped with these disorders related to trauma, rather than the current classification with other anxiety disorders, like panic disorder, generalized anxiety disorder (GAD), and obsessive-compulsive disorder (OCD). In addition, the trauma-spectrum model represents a multilevel approach to nosology, in that biological (i.e., fear circuits), environmental (trauma), and social aspects (social support or the lack thereof) are including in the analysis. This is in contrast to current commonly utilized approaches, which involves a prima facie approach to patients with trauma-related symptoms. This leads to outcomes like the conclusion that all disorders in which anxiety is present should be classified as anxiety disorders.

On the other hand, the multilevel approach does not attempt to create false classifications based on a single factor, like neurobiology. This is in contrast to approaches that, for example, assume that only inherent neurobiological factors influence the development of mental disorders, and attempts to force groups of symptoms into discrete entities that are presented as only related to specific brain pathologies. The deliberations around the formation of the Diagnostic and Statistical Manual-V (*DSM-V*) often took the tack of trotting out brain biologies as a scientific foundation for the classification of mental disorders. This approach often points out that Psychiatry (the *DSM* is a publication of the American Psychiatric Association) is one of community of medical specialties, and psychiatric illnesses should be approached in the same way that, for instance, diabetes is approached by endocrinologists. According to this approach, an illness (diabetes) is caused by a specific defect in physiology (shortage of insulin, or resistance of the tissues to the effects of insulin), and is treated by repairing the defect (giving insulin injections). Thus, the body is able to transport glucose (sugar) into the tissues of the body, which need it as energy and to function. Through the treatments, symptoms of mental confusion, increased urination, and weakness are avoided, and the long-term consequences of poor glucose control, like hypertension and eye and kidney disease, are reduced or eliminated. The patient sees the doctor on regular occasions, where he undergoes laboratory testing and physical examination, and the doctor makes adjustments to the treatment, and writes a prescription for more medication, which the patient gets filled at the pharmacy. In a similar manner, the psychiatrist would treat a patient for a disease (depression) that is related to a physiological defect (shortage of serotonin in the brain) with a medication to correct the deficiency (selective serotonin reuptake inhibitors, or SSRIs). These medications work by increasing serotonin in the brain, relieving symptoms of depression, and avoiding the long-term consequences of depression, like suicide, or disruptions in work or family life. The patient visits the doctor on a regular basis, where he or she is assessed for symptoms, adjustments in the medication are made, or perhaps the medication is substituted for another if the response to the treatment is poor, the doctor writes a prescription for more medication, and the patient gets it

filled at the pharmacy. This fits with a rational or medical approach to mental illness, reassures the doctor, and possibly the patient, is not too expensive and therefore endorsed by the insurance industry, and fuels a profitable health-care industry in pharmaceuticals, laboratory testing, and outpatient psychiatry.

The only problem with the medical model approach to mental illness is that it doesn't really work. For one thing, the serotonin deficiency model of depression is not accurate. It is based on a mythology that depression is simply a shortage of serotonin that can be fixed by increasing serotonin in the brain with a medication like Prozac. If that were the mechanism, why does it take two to four weeks for Prozac to work, since serotonin is increased after the first couple of doses? Neuroscientists and psychopharmacologists have understood for years that the serotonin replacement hypothesis does not explain the data. In fact, illustrations of medications working by boosting neurotransmitters have largely been relegated to advertisements for pharmaceuticals in magazines, and are no longer seriously considered by psychiatric and neuroscience researchers. Academic psychiatry, however, has largely stood by silent while the serotonin replacement model is promulgated by the pharmaceutical industry through its advertising endeavors. The serotonin replacement model is simple and easy to understand, and makes logical sense. It is easy to convey through colorful illustrations and one-line descriptions. The pharmaceutical companies traditionally have provided as much funding for research to academia as have government entities, so there was no incentive to set the record straight about how patients with depression respond to treatment. The serotonin replacement model also fit with the agenda of psychiatry, which has evolved into an industry of 15-minute visits that are reimbursable by insurance companies. It was easier in this short time period to present the disorder and its treatment in simple terms, and avoid complicated discussions of life circumstances and personal feelings that are difficult to conclude in a short period of time. Many clinicians also probably tell themselves that it is best not to open the can of worms and that patients are better off not delving into psychological areas for which there is not an easy resolution. In fact, this line of thinking is reasonable, since exploring the causes of mental illness that have to do with the individual often requires long term psychotherapy treatment for a proper resolution, and most people cannot afford this.

The neurobiological model of mental illness has other problems. Adherence to biological models like the serotonin replacement hypothesis, or other models that only consider neurobiology, leads to a situation where psychiatrists are forced into defending or proving a model that is essentially indefensible. This results in a straw man argument, where psychiatrists are set up as proponents of the biological model, and if the model fails this taken as proof that mental disorders are not valid. Antipsychiatrists and others hostile to the mental health field pour through the breach, resulting in a circling of the wagons, where any critical discussion within the field of psychiatry is discouraged, or even squelched. As an example of this, in 2012–2013 the committee charged by the American Psychiatric Association to come up with the next version of the *Diagnostic and Statistical Manual*, 5th ed. (*DSM-5*), held closed sessions and required committee members to sign non-disclosure agreements. External feedback was invited only after the committee had essentially come to final decisions. This led to both the heads of the *DSM-III* committee, Dr. Robert Spitzer, and the head of *DSM-IV,* Dr. Alan Francis, to write editorials and make public comments critical toward the process. Similar comments came from the American Psychological Association and the British Psychological Association. The criticism has also been raised that there may be no point in developing a revision of the prior version of the *DSM* when there is no new significant information upon which to based changes in the criteria for the psychiatric disorders.

The approach of the *DSM-5* committee is needless to say antithetical to academic tradition. This process is based on unbiased inquiry, rigorous scholarship, and the free exchange of ideas. To retain legitimacy, the scientific process requires careful scholarship, openness to new information, objective observation, lack of bias, a willingness to engage in vigorous debate, and above all transparency. The persistence of the *DSM-5* committee in the face of criticism, including from some of the leaders of academic psychiatry who chaired previous committees, showed an utter disregard for the scientific and academic process. The group's insistence on sticking to a rigid medical framework forced it to abandon the scientific process on which the framework was supposedly founded.

Another problem with the medical disease model is that it requires that psychiatric disorders be discreet from one another. If there is overlap, as naturally occurs for mental disorders, advocates of the biological disease model are forced to use terms like high comorbidity to account for the fact. The use of this term implies that these are discreet disorders, and the fact that they tend to occur together sometimes is treated as an anomaly. That would be like saying, "You sort of have a diabetes–hyperthyroidism condition." Not only is there high comorbidity between disorders, but also the actual symptoms also overlap.

The authors of the *DSM* partially sidestepped this issue but using different ways to describe the same phenomena. For instance, the symptom of feeling cut off from others in PTSD is analogous to the withdrawal or psychomotor retardation seen in depression. Many other symptoms, including sleep disturbance and irritability, are the same. Thus it can be seen that the trauma spectrum model more accurately described the nature of mental disorders as they exist in real clinical practice than the medical model of *DSM*. In fact, this is why many clinicians do not actually use *DSM* in their clinical practices, unless they need to use it for insurance billing or to justify the use of psychotropic medications.

The trauma-spectrum model obviates the problems of the medical model by accepting the fact that there is a spectrum of symptoms following psychological trauma. Patients with different disorders will have overlapping symptoms. This does not obviate the fact that there are also important differences between these disorders. An example of this related to neurobiological studies is reviewed in more detail below.

The medical model-based serotonin replacement hypothesis of depression fails in other respects. There is not room in the model to account for the complex array of factors that contribute to mental disorders. One important factor in the development of depression is the role of previous exposure to traumatic events, especially in childhood, which is often associated with the development of depression in adulthood (CDC, 2010; de Vries & Olff, 2009). Considering the interaction between traumatic experience and developmental stage of the individual at the time of the trauma is crucial to a proper understanding of the presentation of the patient. Developmental stage is important not only because the stage of development of the brain influences how the individual assimilates traumas and other experiences. The psychological profile of the individual, influenced by stage of psychological and social development at the time of the trauma, also plays a critical role.

Another disadvantage of a biological model like the serotonin deficiency hypothesis is that it leaves the individual in the recovery process. This is critical, because factors related to the individual, like motivation and self-growth, are amongst the most important variables in successful recovery from mental disorders. Medical models of mental illness tend to disempower the individual and remove the role of individual meaning and motivation in the process of recovery. The process of disease and recovery is relegated to a battle of chemicals, where the addition of new ones in the form of medications is expected to counteract problems with the ones in the brain. Not only is the individual removed from the process of recovery, it also trains people to be passive and fatalistic. Doing so takes away the possibility of enlisting the individual in recovery (other than asking them to remember to take their meds). Problems like PTSD and depression that are caused by traumatic events respond to processes like psychotherapy, journaling, and discussions with people in the support system who provide positive and empathic responses (although the opposite can have a negative effect). In addition, the biological model removes the process of individual meaning, effectively dehumanizing the individual in the process. This is in part why there has been a backlash against modern psychiatry in the form of the rise of the anti-psychiatry movement.

An example of this dehumanizing process is the medicalization of grief. Previous versions of the *DSM* listed bereavement as an exclusionary criterion for the diagnosis of major depression. The new version of *DSM-5,* however, has eliminated this exclusion, effectively forcing those who have had lost loved ones to either bypass the normal grieving process, or be labeled as someone with a mental illness. This carries with it the risk of being prescribed an antidepressant medication that the person may not need, and which may be associated with potentially dangerous side effects. The medicalization of the grieving process has put psychiatry into the odd role of blunting personal growth and development, when they are supposed to be stewards of mental health. That is because the normal grieving process has to take place for a person to grow through adverse life experiences and recover the capacity to form healthy future relationships. Those who are not allowed to grieve normally become limited in their ability to express a full range of emotions in the future. In fact, the process of responding to trauma can be conceptualized as an extended grieving period, in which the individual advances through individual stages of grief/recovery, and often circles around to begin the process from the beginning, strengthened by what one has learned in the earlier phases. Thus the creation of models like the serotonin replacement hypothesis represent a form of psychiatry declaring war against the processes that are needed for a full recovery from trauma.

The trauma-spectrum model is not presented as the only or best approach to psychiatric nosology, but rather as an example of an approach that can incorporate neurobiology without becoming a prisoner to it. Similarly, antidepressants are not considered to be the enemy, but it is considered essential to take an approach to medication that fits with the data, and to see psychopharmacology as one of many potential pieces of the recovery model, and not as a unique source of potential recovery.

For the trauma-spectrum model to be useful and relevant, it should be able to be used on multiple levels of interpretation. In other words, it should have relevance at the intrapsychic, psychological, clinical, interpersonal, social, philosophical, research, biological, and other levels. Its relevance on a psychological and intrapsychic level is illustrated by the fact that traumatic events, and the response to these events, are typically seen as major watersheds in people's lives. Traumatized people can learn, through reading, journaling, or participating in psychotherapy, that their thoughts, feelings, and behaviors may not be the result of being a bad person or having something wrong with them. Additionally, not viewing themselves as having only a medical disorder gives them more power and control, and brings them personally into the treatment picture. Similarly, on a clinical and research level, the trauma spectrum approach obviates the problems with high comorbidity and frees the clinician to focus on the client–patient as an individual rather than a collection of symptoms or diagnoses.

The trauma spectrum model also has relevance on a neurobiological level. The model predicts that brain circuits and systems involved in the stress response will be similarly affected in these disorders. Specifically, brain areas involved in fear and memory, like the amygdala, hippocampus and medial prefrontal cortex, and neurohormonal systems like cortisol and norepinephrine, should show similar alterations in these disorders that are not seen in anxiety disorders not related to trauma. In a series of studies we and others showed smaller hippocampal volume in patients with a history of childhood abuse and the diagnoses of PTSD (Bremner, Randall, Scott, et al., 1995) (see Figure 9.2), women with BPD and early life trauma (Driessen et al., 2000; Irle, Lange, & Sachsse, 2005; Schmahl, Vermetten, Elzinga, & Bremner, 2003), and women with abuse and DID (Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006). Women with abuse and BPD (Driessen et al., 2000; Schmahl, Vermetten, et al., 2003) and women with abuse and DID (Vermetten et al., 2006) also showed smaller amygdala volume, which is not seen in PTSD. Women with early childhood sexual abuse and depression had smaller hippocampal volume compared with women with depression without early abuse, and nonabused nondepressed women (Vythilingam et al., 2002). Patients with another anxiety disorder, panic disorder, did not show a reduction in hippocampal volume (Vythilingam et al., 2000), and other studies have not consistently shown smaller hippocampal volume in obsessive-compulsive disorder (OCD) or other anxiety disorders (Bremner, 2005a; Cannistraro & Rauch, 2003).

Patients with trauma spectrum disorders show other areas of overlap in terms of neurobiological profile. Both patients with PTSD or BPD related to childhood abuse show alterations in function of the hypothalamic-pituitary-adrenal (HPA) axis, and a functional dysregulation of the prefrontal-limbic axis (Donegan et al., 2003; Driessen et al., 2004; Juengling et al., 2003; Lange, Kracht, Herholz, Sachsse, & Irle, 2005; Schmahl & Bremner, 2006; Schmahl, Elzinga, et al., 2003; Schmahl, McGlashan, & Bremner, 2002; Schmahl, Vermetten, Elzinga, & Bremner, 2004a; Schmahl, Vermetten, Elzinga, & Bremner, 2004b). The trauma spectrum model, however, does not dictate that these disorders are synonymous, or that there should be no differences in neurobiological profile. Just as there are overlapping symptoms, with some symptoms being unique to a particular disorder, it is predicted that there will be areas of both overlap and difference in neurobiology. For instance, we found important differences in neurobiological profiles between women who, although they had similar childhood sexual abuse experiences, in adulthood developed different mental disorders, namely PTSD or BPD.

Our studies showed that BPD and PTSD patients have important differences in the types of stimuli that provoke physiological reactivity (Schmahl, McGlashan, et al., 2002). Women with a history of childhood sexual abuse, some of whom had PTSD and others BPD, were read scripts of both an abandonment experience (being left alone in a shopping mall) and of their specific traumatic childhood sexual abuse experience. Physiological responsiveness was measured with galvanic skin response and heart rate, measures of sympathetic nervous system function. Even though both groups had been exposed to similarly severe childhood sexual abuse, the BPD subjects responded to reminders (scripts) of abandonment but not trauma, and PTSD subjects had the opposite response (Schmahl, Elzinga, et al., 2004). Additionally, we found that abused women with PTSD presented with scripts of their childhood abuse experiences had decreased frontal lobe function (Bremner, Narayan, et al., 1999). Abused women with BPD, however, did not show this decrease with traumatic scripts (Schmahl, Elzinga, et al., 2003), although they did show decreased function in the frontal lobe when presented with scripts of an abandonment scenario (Schmahl, Elzinga, et al., 2003). These studies illustrate that neurobiological profiles highlight differences in the disorders that are clinically relevant.

These are just a few of the biological findings that are relevant to the concept of trauma spectrum disorders. The findings are consistent with a common neurobiology and neurocircuitry underlying the trauma-spectrum

disorders, including PTSD, DID, BPD, and depression related to early abuse. There are some commonalities in neural circuitry involving the prefrontal cortex and hippocampus, although there are important differences, such as differences in physiological reactivity to different types of traumatic or stressful reminders. This is consistent with the fact that there are both overlapping symptoms, as well as areas of symptomatic difference, in patients with these disorders. We discuss the neurobiology of stress in more detail later in the context of a multilevel analysis approach.

In recent years the term trauma-spectrum disorders has been used to include not only stress-related mental disorders but also mild traumatic brain injury (mTBI). This has mostly arisen as a result of the war in Iraq and Afghanistan with the large increase in returning soldiers affected by PTSD and/or mTBI. An increase in exposure of soldiers blast explosions from improved explosive devices (IED) is responsible for many of the cases identified as mTBI. This use of the term trauma spectrum disorders creates a convenient category of disorders that are of particular relevance to the Department of Defence (DOD) and the Veterans Administration (VA), PTSD and mTBI, since they are two of the most common disorders in soldiers returning from Iraq and Afghanistan, and are of major public health relevance and importance to the DOD and VA. PTSD and mTBI, however, overlap in terms of diagnosis, clinical presentation and treatment (Cifu, Cohen, Lew, Jaffee, & Sigford, 2010; Jaffee et al., 2009; Kennedy et al., 2007). MTBI is defined as a loss of consciousness following a blow to the head or sudden acceleration/deceleration, loss of memory for events before or after the event, a change in mental state (feeling dazed, disoriented or confused), or a focal neurological deficit that may or may not be transient (Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine, 1993). Structural changes on brain imaging are not seen with mTBI. Cognitive symptoms often seen in PTSD patients, like headache or memory and concentration problems, are also seen in mTBI (Levin et al., 1987), which complicates diagnosis. Furthermore, rates of PTSD are increased following accidents with head injury (Walilko et al., 2009).

The use of the vague language categorizing mTBI as secondary to blast associated with any changes in mental state has thrown a broad net over soldiers returning from overseas. The most recent criteria do not require loss of consciousness, so virtually everyone who experiences a blast followed by the fog of war and later has problems with headaches or memory loss will meet criteria for mTBI. Many of these soldiers probably never had an actual brain injury, since exposure to blasts is less likely to injure the brain as a blow to the head or a car accident with rapid acceleration–deceleration that is more dangerous to the brain. Because of symptom overlap, symptoms of PTSD or mild stress reactions may be misattributed to mTBI, which complicates diagnosis and treatment.

Another dilemma in the field of PTSD and mTBI has been the question of the diagnosis of PTSD in cases of mTBI where there has been a loss of memory for the traumatic event. This is complicated by the fact that the requirements for intense fear, horror, or helplessness at the time of the event are technically not met (Bryant, 2001, 2008). Clinically, many patients develop PTSD after accidents for which they have no memory, possibly related to the formation of trace memories or memories not readily accessible to consciousness (Fani, Hampstead, & Bremner, 2006; McMillan, 1991). A consensus in the published literature, however, has arrived at the conclusion that PTSD can occur in the aftermath of brain injury events for which there is no conscious memory (Bryant, 2001; Harvey, Brewin, Jones, & Kopelman, 2003; Jones, Harvey, & Brewin, 2005; Mollica, Henderson, & Tor, 2002; Sumpter & McMillan, 2005).

The use of the term trauma-spectrum disorders as a description of both mental disorders related to psychological trauma and neurological brain disorders such as mTBI is problematic for a number of reasons. First, it is not possible to construct a valid rationale for the grouping of these disorders, other than as samples of convenience, or topics that should be given a high priority by governmental agencies. The construction of diagnostic criteria based on worthiness to receive government services or resources or for administrative convenience of course lacks scientific validity. One might speculate that this version of trauma-spectrum disorders was conceived as having a common neurological etiology, or an effort to bring trauma-related mental disorders into the spectrum of brain-based diseases. This approach, however, again runs into the problems that occur when emphasis is placed on a single factor in the development of a stress-related mental disorder.

Inclusion of mTBI in the group of trauma spectrum disorders has many of the same problems as the serotonin deficiency model. This revised trauma spectrum model emphasizes a common etiology of the disorders in neurology. The implication is that similar neurological pathways are involved in, say, PTSD and mTBI. However, the pathophysiology of PTSD involves fear circuits of the brain (amygdala, medial prefrontal cortex and hippocampus) and processes of learning, while mTBI

potentially involves shear injuries of neuronal processes that are most concentrated in the temporal lobe. Again, a singular focus on the neurological aspect of the disorders means that appropriate consideration is not given to other levels of analysis discussed above, such as the role of the personal experience and response in the aftermath of psychological trauma. This and the many other factors that were articulated above are critical to the understanding of the development of trauma-related mental disorders. Attempting to acquire acceptance for mental disorders by repackaging them as neurological disorders limits the ability to obtain a comprehensive assessment and therefore arrive at an appropriate treatment.

Trying to differentiate mTBI and PTSD may introduce an artificial dichotomy. Many soldiers exposed to blast also develop PTSD or other stress-related mental disorders. Since one of the factors contributing to PTSD is seen to be changes in neurobiological systems, there is no need to differentiate symptoms like memory loss in returning soldiers as related to a brain-based disorder (mTBI) versus a psychological disorder (PTSD). The multiple levels of analysis perspective, however, do not require such a distinction. Not focusing on make a dichotomous decision between two supposedly distinct disorders ultimately results in the best treatments for the patient. This was the consensus of a conference of PTSD and mTBI researchers and clinicians sponsored by the Department of Defense (DOD) in 2012. In other words, in the end it doesn't matter what causes the symptoms if the treatment is the same.

RELEVANCE OF THE MULTIPLE LEVELS OF ANALYSIS APPROACH TO DEVELOPMENTAL PSYCHOPATHOLOGY

An important part of the multilevel approach is an emphasis on the importance of development on the response to psychological trauma. As the individual moves from infancy through childhood and adolescence to adulthood changes take place on a psychological, social, behavioral, and neurological level (Feiring & Lewis, 1996). Different people may travel different developmental paths and end up at the same place (equifinality), or travel the same path with different ultimate outcomes (multipotentiality) (these concepts are discussed in greater detail below) (Cicchetti & Dawson, 2002; Cicchetti & Rogosch, 1996). An example of this is the fact that two people can be exposed to similar childhood traumas, but only one develops depression or PTSD in adulthood. The reason for these differences are not always clear, but factors such as individual resilience likely play a role (Vythilingam et al., 2009). Another example of this is the finding that some women arrive at the outcome of depression in adulthood following a history of childhood abuse, while other women develop depression without a history of abuse. An interesting clue related to this phenomenon is that women with a history of abuse and depression compared with both nonabused depressed women and nonabused, nondepressed women have smaller hippocampal volume on magnetic resonance imaging (MRI) (Vythilingam et al., 2002) and potentiated cortisol reactions to stress (Heim et al., 2000). This suggests a biological difference in the two groups of women, even though they have a similar nosology (i.e., symptoms of depression). Thus there may be an abuse-driven depression and a genetically driven type of depression. Therefore, one can arrive at the final depression end point by two different paths (e.g., early abuse or inherent disposition). Emerging evidence shows that these subtypes have different treatment responses (e.g., early abuse and depression responds more to therapy and less to medication). The use of the multi level assessment is therefore shown to have clinical relevance.

Richters and Cicchetti (also Richters and Hinshaw) have argued that diagnostic categories developed by psychiatry, as exemplified by the American Psychiatric Association's (APA) ever-evolving tome, *Diagnostic and Statistical Manual,* 4th ed., text revision (*DSM-IV-TR*; APA, 2000), represents a potentially false and forced application of the disease model to mental processes and dysfunctions (Richters & Cicchetti, 1993; Richters & Hinshaw, 1999). Following the one gene, one biological defect, one disorder model, psychiatric nosology, as discussed above, represents mental disorders as synonymous with medical disorders. According to this model, mental disorders represent harmful dysfunctions, that by implication are related to errors of evolution that lead to faulty genes manifesting in disorders (Wakefield, 1999).

The medicalization of mental disorders over the last few centuries can be interpreted as an extension of the cultural and societal response to the mentally ill. The etiology of mental disorders was once viewed as manifestations of evil spirits, infestation by the devil, or witchcraft. Although many cultures continue to harbor similar beliefs, for the most part in countries like the United States this is no longer the case. Patients with mental illness, however, continue to suffer from considerable stigmatization. The medical model was probably conceived by some good-intentioned clinicians as providing a framework whereby patients with mental disorders could avoid judgment as being inherently weak or morally defective

individuals. This is one advantage of the medical model, in that mental disorders can be presented to the patients as well as friends and family as brain-based diseases that are not their fault, just as someone should not be blamed for developing diabetes. The negativity and stigmatization associated with the personal blame approach can further hinder the recovery of patients from mental disorders, and offering this alternative way of looking at the disorder can be quite helpful in assisting patients in their recovery. The multilevel analysis approach takes advantage of the helpful approach of using neurobiology to further patient education and give traumatized patients a conceptual framework to understand their disorders in a way that reduces self-blame and fear. The fact that this framework is still imperfectly employed, however, is shown by the persistent stigma against people with mental disorders that continues to exist in our culture.

The medical model has seen limited application by clinicians who are actually at the front lines of providing treatment for patients with trauma-related mental disorders. Many clinicians complain that the application of psychiatric disorders based on strict criteria is not helpful in the clinical practice, where more nuanced assessments are required to deliver the maximum therapeutic benefit. Many clinicians continue to flock to the professional association meetings where they sit in rapt attention while their counterparts in the world of to them about the medical model of psychiatry. This psychotic split led to the situation where if asked directly clinicians would say something like, "I don't use the *DSM* in my practice, I just need to get a code (that corresponds to a specifically defined psychiatric disorder) to bill insurance with." Although clinicians are taught to diagnose a single condition and apply a single remedy, in the real world of clinical practice, faced with the inadequacy of this approach, they usually end up treating clusters of symptoms, or deal with patients on a one-to-one basis, as individuals.

The process of incorporating psychiatry and mental health treatment into the medical fold has never been completely achieved. This may be due to a number of factors, including persisting stigma, suspicions amongst the other medical professions that mental disorder weren't actually equivalent in nature to the medical disorders they were treating, or qualms about the reliability of the scientific foundation for the disorders. When a specific etiology of what was previously viewed as a mental disorder is identified, like a B12 deficiency for dementia, it tends to be transferred from psychiatry to other fields like neurology. For example, Parkinson's Disease originally was not recognized to be a disorder of dopamine deficiency related to degeneration of dopamine neurons in the striatum. Similarly, epilepsy was originally felt to be secondary to possession by evil spirits. It was only with the advance of medical science that the true etiology of epilepsy was discovered, namely that seizures were related to abnormal bursts of neuronal firing which caused damage in the hippocampus and other brain areas, increasing susceptibility to future seizures.

In the face of mounting challenges to the medical model of psychiatry, academic psychiatrists have responded by pulling the wagons into a circle and ratcheting up the defense of the model. They also attempt to deal with criticisms of the model by a continual tinkering with the diagnostic structure. Tomes like the *DSM* get progressively larger with successive editions as the number of diagnosable mental conditions expands exponentially. Indeed, the criticism has led to the conclusion that there is not time to wait for each successive version of the *DSM*. Rather, new versions of diagnostic criteria should be sent out into the field, like successive updates of software program, to find glitches in their actual use that will allow further tinkering back in the halls of academe. Never mind that no one would ever buy software made by a company with a business model of using its customers to test the software for bugs. The pharmaceutical industry, of course, have been ardent supporters of the medical model and associated institutions like the *DSM*. To not do so would probably be corporate malpractice, or a violation of their fiduciary duty to their shareholders, as there is so much potential for profit in a system that emphasizes one diagnosis with one treatment (i.e., an antidepressant), and that has a built in mechanism to continuously increase their market, as diagnostic shifts tend to include a greater percentage of the population in the category of disordered over time. The system also provides an excellent opportunity for companies to mount outreach and awareness campaigns (e.g., marketing shyness as social phobia), as well as provide education to clinicians, the outcome of all these efforts being an increase in their market share for antidepressant medications. As the number of psychiatric disorders multiply, the fact that the treatments remain limited in number is conveniently ignored. The fact that the treatments for different mental disorders is usually the same is also conveniently ignored. At one point Glaxo-SmithKline developed a handy card that it handed out to clinicians, which represented a decision tree to help them arrive at the diagnosis of the appropriate anxiety disorder based on the criteria of the *DSM*. The futility of the exercise, however, was highlighted by the fact that no matter the final outcome, the next step in the algorithm was always

to prescribe Paxil. The irony of such a useless exercise, which ultimately resulted in no effect on the treatment course dictated by the medical model, was apparently not appreciated by anyone involved.

Another argument against the medical or harmful dysfunction model of stress-related mental disorders is based on human evolution. The continued existence of depression and anxiety argues against them being specific diseases in the medical formulation. If they were such disorders, they should have been eliminated from the human species long ago as maladaptive phenomena through the natural selection process of evolution. If anxiety or depression only had the potential for harm that should have reduced the possibility that individuals with these tendencies would survive long enough to reproduce and pass their genes along to the next generation. Human evolution in the strict sense probably ended about 20,000 years ago, although the capacity of humans continued to evolve along with the evolution of culture (Richters & Hinshaw, 1999). The rapid acceleration of cultural evolution made biological evolution obsolete, as evidenced by the total domination of the planet and other animal species by humans, who now use other animals as pets or food, rather than as competitors in the game of natural selection.

Before the development of agriculture, humans were roving the Savannah in small bands of hunter-gatherers. Up until that point, the evolution of the human brain conveyed adaptive advantages, through the development of the capacity for abstract thought, language, and advanced social relationships. Even after the physical evolution of the brain reached its apex, however, the cultural and adaptive functions of the brain continued to evolve. Along with the development of these cognitive abilities came mental phenomena like anxiety and depression. These mental symptoms, however, are not necessarily affected by evolution. They could be accidental by-products of the development of the frontal cortex and other cortical brain areas that gave humans the potential to have such incredible adaptivity to changes in the environment and to continue with cultural evolution even after biological evolution came to a halt. Another possibility is that they are related to behaviors that had survival value, and therefore were selected in evolution. Whatever survival value they had for primitive hunter gatherers on the Savannah, however, is probably lost in the transition to modern culture, which brought with it living in buildings and days spent puzzling over financial accounts rather than chasing animals through the bush.

Symptoms of anxiety and depression may have served specific purposes that benefited humans, at least at one point in history. For instance, if there was a pack of lions in the area where a band of hunter-gatherers was camped, this could lead to an increase in fear and vigilance, which may have made the difference between life and death. These symptoms would persist for long periods of time, possibly after the threat had been removed. Children would sense the type of environment they were born into, and their developmental evolution would be adjusted accordingly. Children in a harsh, deprived, or nonsupportive environment would grow up being mistrustful and socially withdrawn. This might have survival value in protecting the child from potentially harmful persons in the absence of a functional parent to protect them.

Symptoms of depression also probably have had a behavioral function at some point in time. They are a by-product of the development of the capacity in humans to form close social attachments. When those attachments are broken, through death or separation, there is a natural process of grieving where individuals recover from the disruption of the social connection and form the capacity to form new connections. If they do not go through this process, they may not go on to reproduce with others in the future. In addition, depression causes a social withdrawal and decrease in activity. Death of a partner or parent may put the survivor at greater risk without the added protection, so withdrawal from potentially dangerous situations would also have survival value. Similar behavioral effects occur with illnesses such as infections, which probably have similar survival value in allowing the conservation of energy and resources.

Symptoms of anxiety and depression that were adaptive in the past do not necessarily serve an adaptive or helpful role in modern society. The fight or flight response that was critical to survival in the hunter-gather stage of the human species that had real and necessary survival value is no longer useful when we are rarely under actual physical threat. We nevertheless preserve the same stress response systems, but now rather than tiger attacks they are more likely to be triggered by getting caught in traffic or being passed over for a promotion. These stressors lead to the same outpouring of fight or flight neurohormones, even if they are useless for dealing with the present situation. Repeated activations of neurohormonal stress response systems serve no useful purpose in these situations and can only lead to a repetitive wear and tear on the body, or mental suffering in the individual. This perhaps explains the proliferation of books and classes about meditation, Buddhism, and the use of practices like mindfulness, which all boil down to an attempt to turn off the stress physiology system.

The medical model of *DSM* has latched onto the easy catch-all that a mental disorder exists when the requisite minimum of symptoms in different categories results in a significant impairment in work or social function. There are a number of problems with this definition, though. If there is a disruption in the marriage or relationship, how can you be sure it was related to the symptoms? Many people have trouble working or keeping relationships that do not have symptoms of mental disorders. Conversely, some spouses feel an important caretaker role in helping their mental disorder afflicted spouse, especially those with PTSD.

The environment has an important effect on whether or not symptoms of mental disorders reach the point of conditions associated with distress or impairment. The military is a good illustration of this. It isn't uncommon for soldiers to develop PTSD symptoms while in the military, but continue to be able to do their jobs and function normally. In combat arenas where there is a lot of heavy fighting, most of the soldiers will develop behaviors that could be classified as consistent with PTSD symptoms. Being jumpy or easily startled actually has survival value in a combat zone, especially when there is the continual threat of unexpected attack by insurgents. It is only when the soldier returns to the States and is unable to turn off the combat mind that he or she runs into trouble. Behaviors that were adaptive and complementary in one environment suddenly become not so in another environment. Overnight, because of modern jet travel, the person is transported from a combat zone in the Middle East to a leafy suburb in America. Many soldiers report this transition as a shock to the system. Although nothing about the person has changed, the change in venue has suddenly created a mental disorder. Sometimes a soldier returns to the States but remains an active duty soldier or officer. He or she may have symptoms of PTSD but be able to function because the military culture effectively supports the PTSD symptom burden, either because others have similar problems and are understanding, or there is a recognition that the symptoms and behaviors are related to military service overseas, something that is highly valued. In addition, the structure of the military is conducive to the maintenance of mental function. There is a set structure of what to do every day. Proper diet and exercise are regulated, and in fact required. The active duty military person, if they live on base, are surrounded by sympathetic persons, and may have little exposure to civilian life, with its stigma of mental illness. It is only after leaving the service, when the ex-soldier reverts to a poor diet and lack of exercise, there is increased access to alcohol and illegal drugs, and a lack of structure in the day, possibly even unemployment, that symptoms are associated with dysfunction. A similar phenomenon occurs in the civilian sector, where when people lose their job, they suddenly become dislodged and overwhelmed with traumatic memories or other symptoms. The preoccupation with work, and a pattern or working extended days that end in exhaustion and blissful sleep, may have served to keep at bay intrusive traumatic memories. When the busy job or career is removed, the individual is flooded with memories and becomes dysfunctional, or the dysfunction may be related that they seek drugs and alcohol to escape from the memories.

In addition to creating false models of disorders that have no utility in clinical practice, academic psychiatry and psychology have also become hostages of what has been termed the *abduction of disorder by psychiatry* (Richters & Hinshaw, 1999). As mentioned above, in academic psychiatry and the arena of psychiatric research, mental disorders are expected to conform to the medical model, which means that diagnoses should be pure and without comorbidity. When they fail to conform to model, rather than consider that there may be a problem with the model, the onus is put on the researcher to explain the discrepancy. Researchers then go off on a wild goose chase to go up with an explanation that doesn't have to mention the obvious. Namely that, in the trauma field at least, there is overlap of symptoms amongst different trauma-related disorders, consistent with the trauma spectrum model. This leads to some investigators, in the search for a pure disorder, to perform studies on patient groups that are so unusual that they have no applicability to the patients that actually present to clinical practice. For example, trauma patients with pure PTSD, who have no history of depression or other anxiety disorder, no past substance abuse, no medical problems, and preferably not treated with medications.

Studies of the neurobiology of trauma-related disorders, however, do no support the specificity of disorders. This is exemplified by brain imaging studies, but also in the field of genetics, where the data seem to show that genes can confer risk for a range of disorders previously not felt to be related, like attention disorders, psychotic disorders, etc. This is an illustration of the concept of multipotentiality (i.e., that a gene can lead to different disorders depending on the interaction with development and the environment).

The increased risk of physical disorders in patients with trauma-related mental disorders also requires a multilevel analysis. Both depression (Vaccarino et al., 2007) and PTSD (Vaccarino et al., 2013) have been shown to be independent risk factors for the development of heart disease. PTSD has also been associated with a range of other

medical disorders, including infectious diseases, diabetes, and asthma (Anda et al., 2008; Sareen et al., 2007; Zatzick et al., 2010). In addition, PTSD or childhood abuse is associated with increased obesity, which is a risk factor for diabetes, and increased rates of smoking, alcoholism, and drug abuse (Anda et al., 2006; Dube, Felitti, Dong, Giles, & Anda, 2003; Williamson, Thompson, Anda, Dietz, & Felitti, 2002). Therefore the most appropriate way to treat patients with PTSD and victims of childhood abuse is a multilevel approach that considers both mental disorders and physical disorders and does not make artificial distinctions between the two.

To have a proper perspective on the current gridlock our *DSM* era it helps to take a historical view of the mental health field. There is a long history of research in the field of traumatic stress. Popular culture has recognized traumatic stress for even longer. Below the subject of traumatic stress is examined in further detail, from the perspective of the individual, psychology, the context of the individual within society, as well as the effects on neurobiology, stress physiology, and physical health, risk factors and resiliency. This comprehensive approach characterizes the multiple levels of analysis viewpoint.

PSYCHOLOGICAL TRAUMA: THE LONG VIEW

There is a long history of scholarship in the area of traumatic stress. This predates the current era dominated by the *DSM* and its establishment of the posttraumatic stress disorder (PTSD) diagnosis in 1980. Trauma research dates back to 1830, or earlier. That was the time in England when a syndrome called railway spine or railway injuries was first described. Railway spine occurred after train accidents, and the symptoms looked very similar to what today we would call PTSD. It included problems with anxiety, memory loss, confusion, and amnesia. One of its symptoms, back pain, is common to many patients with PTSD, even though it is not part of the criteria for diagnosis (for most patients with back pain a physical etiology is never found; Bremner, 2009).

As described in a paper in the journal *The Lancet* in 1830, Railway spine was considered to be due to small contusions of the spinal cord that were below the limits of detection with the naked eye. This paper described for the first time a disorder caused by a psychological shock or trauma with no apparent physical blow or impact for its cause and no apparent physical injury. The syndrome was fully described in a book by Erichsen called *Railway and Other Injuries of the Spine*.

It was at about this time that psychiatrists in Germany first described what they called traumatic neurosis. The psychiatrist Oppenheim was the first to describe it. He wrote that a psychological stress or extreme shock could lead to long-term changes in physiology in the absence of physical injury. This was the first time that an environmental event was hypothesized to be solely responsible for changes in the brain. In other words, what you visually see, hear, and feel could cause a long-term disorder, a remarkably revolutionary concept at the time.

World War I (WWI) with its massive number of physical and psychological casualties saw the development of the concept of shell shock. This disorder, which affected soldiers in combat, was associated symptoms of becoming confused on the battlefield, and forgetting one's name or identity. The development of the concept of shell shock is similar to that of railroad spine, in that it originally was thought to be caused by the exploding of shells in proximity. However, it was observed some cases developed when the shells were far away (i.e., that a physical cause was not necessary for the development of the disorder). This led to the idea that the psychological trauma of combat could be the cause.

Freud was coming into prominence at this time and eventually his views would dominate current views on symptoms associated with trauma. Freud came up with the term combat neurosis to describe soldiers who developed mental symptoms in combat. In Freud's view it was caused by a suppressed urge to run from the battlefield. Combat neurosis was an extension of Freud's views that mental disorders were caused by unconscious conflicts that came to the surface in the form of symptoms. In the case of soldiers, the controlling ego battles to suppress primary instincts for self-preservation. This removed the possibility that the actual stress of war could be the cause. This fit with the agenda of governments at the time who were focused on keeping soldiers on the battlefield and were not interested in taking responsibility for the fact that they were creating tens of thousands of psychiatric casualties by exposing them to war. On the civilian front, Freud similarly applied his theories to explain the neurosis of his famous patient, Anna O., whom he first described as being the victim of sexual abuse by her father. In his reformulation there was no actual sexual activity, it represented repressed desires to have sex with her father and kill her mother, or the so-called Oedipal complex. The history of the next few decades of psychiatry, especially in the United States, was characterized by the total dominance of psychoanalysis. This left no room for the trauma of life in the development of mental disorders. There was little or no discussion of

the role of environmental events like psychological trauma on mental health.

The next chapter in the history of American academic psychiatry was the rise of biological psychiatry. Freud used the language of physics to describe the forces of the unconscious and the ego and superego in his model. However, by the 1970s psychoanalysis was viewed as being unscientific and not testable using the methods of science. In fact, psychoanalysis is more akin to a cultural entity than a hard science, which is why it has long been of interest to scholars in the arts and humanities. The supposed nonscientific, nonmedical nature of psychoanalysis was used by the biological psychiatrists who used it to take over leadership of the psychiatry departments in the universities and medical schools from the analysts.

To pull off this coup, however, the biological psychiatrists had to use their alliance with other disciplines in the medical sciences. They employed the common lingua of neuroscience and genetics, a language that all physicians and medically trained scientists understood and could communicate with. Another advantage of this approach was that the psychiatrists were able to exclude psychologists and others without formal medical training and thus consolidate their hold on power. Previously, in the world of psychoanalysis and psychotherapy, psychologists and social workers could compete equally, however now they suddenly lacked the training and expertise needed for this new role in this new age.

The arrival of the biological psychiatrists brought with it the expectation that a medical basis would soon be found for mental disorders. This was anticipated to parallel, for example, the discovery that a shortage of insulin was responsible for the puzzling symptoms of diabetes, which included excessive urination, feeling hungry, and thirst. The discovery of the cause would be followed by the invention of a cure. This was and continues to be paralleled in the media, which presents this view of psychiatry in the popular press. Although other medical specialties paid lip service to the new discipline of medical psychiatry or neuropsychiatry, they continued to harbor unexpressed misgivings that these disorders were equivalent to those in their own specialties.

The initial focus of the biological psychiatrists was on schizophrenia, which they viewed as a real disorder. The focus of the first editions of *DSM* was on schizophrenia and to a lesser extent major depression. The descriptive language of psychoanalysis for disorders related to anxiety, dissociation and somatic disorders, was not extensively modified, probably related to the unspoken belief that there was not a solid scientific basis for these disorders. For instance, there was long a resistance to the use of the diagnosis of PTSD, to the extent that 10 years after its introduction to the *DSM* in 1980, it was rarely used to apply to combat veterans with mental disorders (Bremner, Southwick, Darnell, & Charney, 1996). Dissociative disorder diagnoses continue to be met with skepticism by many clinicians. This was the basis for the fact that the initial editions of *DSM* continued to use the language of the neuroses.

The *DSM* was designed to have a collection of diagnoses that were not based on specific etiologies. This was an attempt to break psychiatry free from the grasp of psychoanalysis, which had a descriptive model that entailed all psychiatric disorders. This created, however, an inherent paradox, since the medical diagnosis is based on the etiology of the disorder. How could it be possible that major depression was a medical disorder, just like diabetes, when it wasn't known what caused it? One way to side step this problem was to assert that the etiology would soon be found, but in the meantime we needed specific criteria for diagnosis to further research on these disorders and standardize the field.

DSM-III, published in 1980, saw the final elimination of the language of psychoanalysis from psychiatric diagnosis. In its place came specific lists of mood and anxiety disorders described in neutral language. The development of *DSM-III* occurred at the time when soldiers were returning from Vietnam, and were clamoring for treatment and recognition of the mental symptoms they were suffering from in the aftermath of the war. This led to the description of a Vietnam War syndrome. The first edition of the *DSM* had gross stress reaction described as an acute reaction to the stress of combat, that were assumed to be transient in nature. If symptoms persisted this was considered to be secondary to a preexisting psychopathology or personality disorder. Based on this concept the military tried to screen recruits for personality problems to avoid stress reactions on the battlefield and enhance the fitness of their soldiers. Discussions about the etiology of the Vietnam War syndrome reintroduced the debate about whether psychological trauma in and of itself could cause lasting mental disorders.

Acknowledging that war caused mental illness would mean that the government was responsible for afflicted soldiers. This had political and societal implications. It was determined that objective research in the field of psychological trauma was needed to resolve this issue. Objective rating scales were developed to measure quantity of exposure to combat trauma and severity of mental symptoms. Studies did show that degree of combat exposure was

correlated with severity of PTSD symptoms (Keane, Caddell, & Taylor, 1988; Keane, Wolfe, & Taylor, 1987). Eventually the model that combat can cause mental disorders prevailed. This led to the inclusion in the *DSM-III* in 1980 of PTSD, emphasizing for the first time in the twentieth century the central role of trauma.

The struggle for recognition of the central role of trauma in the development of PTSD, however, was associated with its own problems. Proponents of the model became resistant to the idea that anything other than combat trauma was responsible for PTSD in veterans. Because of this there was resistance that other factors, such as a history of childhood abuse (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993) or genetics (Goldberg, True, Eisen, & Henderson, 1990), could contribute to severity of PTSD. Accumulating research, however, demonstrated several factors that increase the risk for PTSD after trauma, including prior traumatization and mental disorders, social support, education, and age at the time of traumatization (Brewin, Andrews, & Valentine, 2000).

PTSD is the only disorder in the *DSM* that includes the presence of psychological trauma exposure in the criteria for the diagnosis. It is not the only disorder, however, that has an important link to trauma. As reviewed above, other disorders, including dissociative disorders, borderline personality disorder, and in cases of childhood abuse, depression, are also linked to trauma exposure (Battle et al., 2004; Bohus, Schmahl, & Lieb, 2004; Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004; Schmahl, McGlashan, et al., 2002; Zanarini, 1997; Zlotnick et al., 2003).

The requirement for trauma exposure was included in the "Criterion A in the criteria for PTSD, which first appeared in *DSM-III*. Defining psychological trauma, and stress in general, is not necessarily a simple exercise. Should it be based on an objective assessment of the impact of a trauma, or how it affects the individual? If it is objective, who will decide what constitutes a severe trauma? Psychiatrists? Does that paternalizing situation where the field of psychiatry determines who is and is not mentally ill and what shall be done about it? In the legal arena, the concept of vulnerability is described as the eggshell skull, i.e., someone may be more prone skull fracture than others. The first version of *DSM* that addressed the issue defined psychological trauma as an event beyond the range of normal human experience.

Subsequent research, however, showed that most people are exposed at some point to events like car accidents, robbery, assault, and abuse (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). The criterion was so all inclusive that it was essentially useless. In DSMIV the criterion was revised to include "exposure to a threat to life to self or significant other accompanied by intense fear, horror or helplessness" (pp. 1–17) (Saigh & Bremner, 1999). Using the new diagnosis of PTSD it was found that 8% of people in the United States suffered from PTSD as some point in their lives, with women affected twice as often as men (Kessler et al., 1995). In women PTSD is most commonly related to childhood sexual abuse, and physical assault in men (Kessler et al., 1995). Subsequent research showed that PTSD related to civilian traumas such as child abuse affected a far larger number people in the U.S. than combat veterans (MacMillan et al., 1997). The development of specific criteria, although not without its problems, allowed for an expansion of research in PTSD.

In conjunction with the development of the concept of Vietnam War syndrome, other trauma-related syndromes were being identified. For instance, clinicians described a rape syndrome in female rape survivors, and battered child syndrome in victims of childhood abuse. Also, different countries felt that their collection of symptoms related to their own particular wars or genocides were unique to their culture. Subsequent research, however, has shown that symptoms of PTSD are stable across cultures, with perhaps the main difference being how one interprets the meaning of the symptoms based on one's culture (Kirmayer, Lemelson, & Barad, 2007).

DSM-III PLUSES AND MINUSES

The advent of PTSD and psychological trauma in *DSM-III* had benefits in terms of ability to do research, however in some ways it was a Faustian bargain. As mentioned above, the *DSM* freed itself from psychoanalysis and in the process created a series of stand–alone mental disorders defined only by the face value of their presenting symptoms. What resulted was a series of disorders that in fact have many overlapping symptoms. Some symptoms are very similar, if not identical, between the disorders, although they may have received slightly modified descriptions. For instance, hyperarousal in PTSD could be seen as equivalent to psychomotor agitation in depression. Also, the flashbacks seen in combat veterans with PTSD were considered to be unique to the disorder, although in fact they are traumatic memories recalled in a dissociative state, similar to the dissociative disorders. The impetus behind promoting the diagnosis of PTSD in veterans as combat trauma related was associated with a resistance to association with other disorders that might not have the same prestige, or were considered marginal, like the

dissociative disorders. Also, clinicians and researchers focused on the different trauma-related disorders attended different meetings and belonged to different societies. This led to the development of different camps associated with the different disorders.

The trauma-spectrum model discussed above calls for a grouping of mental disorders linked to traumatic stress (Bremner, 1999, 2002a). The model explains the development of mental disorders based on a pathway where stress interacts with genetics, as well as personal, developmental, social, and other factors to produce stress-related psychiatric disorders. Bremner used the model to argue for inclusion of disorders related to trauma in a separate diagnostic category (Bremner, 1999, 2002a). The argument was made that the classification of PTSD as an anxiety disorder did not make sense from either a nosological, clinical, or biological level, as it shares little in common with the other anxiety disorders other than the symptom of anxiety.

In a series of studies, we and others showed that the trauma-spectrum disorders share important neurobiological fingerprints that differentiate them from the non-PTSD anxiety disorders. The neurobiology of obsessive-compulsive disorder, and to a lesser extent generalized anxiety disorder (GAD) and panic disorder (PD), are different from PTSD. For instance, brain imaging studies have implicated brain areas like the striatum in OCD, while the trauma disorders are more linked to the amygdala, hippocampus, and medial prefrontal cortex (Bremner, 2004, 2005a). Although some cases of depersonalization disorder have been reported where there is no obvious traumatic etiology (Simeon et al., 2000), essentially all patients with dissociative identity disorder (DID) have a history of severe childhood abuse (Vermetten et al., 2006).

TRAUMA AND THE SELF

One of the things that has been lost in the medical model of trauma and PTSD is the importance of the impact of the event on the individual. People develop a sense of personal meaning around their trauma experiences. Trauma may also make people come to believe that life has no meaning, however this is still a personal belief or value system. The medicalization of trauma does not encompass the effect of traumatic stress on the psyche, sense of self, character, and individual, considered both as him/herself and within society and culture they are a part of.

Trauma affects the way we view the world and ourselves. Traumatized people sometimes feel that they are somehow to blame for what happened to them, or that they are a bad person. Others may feel that their traumatic experiences are not necessarily negative. Or there may be a process where what was a negative experience is transformed through personal growth and becomes a source of strength and meaning. This has given rise to the concept of traumatic growth, or events that stimulate change and result in a person moving in a different path in life, sometimes with positive results. There are many artists and scientists who have taken their traumatic experience and used it as a source of inspiration and/or motivation. This response to trauma can often be healing.

One important aspect of psychological trauma is how it changes our perception of the world. Most of us go about our daily lives with the illusion that the world is a safe place. We may not even think about it, we just take it for granted. In fact, this is usually a good thing; otherwise, we would be paralyzed by anxiety and would not be successful in our endeavors. No one wants to be able to see into the future. If you knew in advance what was in store for you, it would make it difficult to live in the present. We therefore live in an illusion of safety that makes life easier. When this illusion is shattered by a traumatic event, it makes us realize how transitory life is and what an unsafe world we live in. A woman raped in an alleyway at night will probably never feel that an alleyway is a safe place in the future.

Countries also carry trauma histories with them. A country can respond to a traumatic event with avoidance and numbing and an attempt to forget. Look at Japan in the aftermath of World War II. However, if left alone, psychological trauma can be suppressed for only so long, and may come back later to haunt you (Bremner & Reed, 2014).

Trauma can take on political and societal dimensions. Terrorists use trauma as a political tool. It serves their purpose to violate the personal feelings of safety and security in others, because it challenges the controlling political or social institutions that they seek to overthrow. Targeting mass transit systems that everyone uses, like airplanes or trains, is a reminder that one is always in danger from another terrorist attack. The choices of targets are deliberate. Remember the anthrax scare? We all get letters in the mail.

RISK FACTORS FOR THE DEVELOPMENT OF TRAUMA-RELATED PSYCHOPATHOLOGY

One variable to consider in a multilevel analysis of psychological trauma is risk factors for the development of trauma-related mental disorders. About half of people or

more will be exposed to a psychological trauma at some point in their lives (Kessler et al., 1995). Only about a quarter or less of people develop PTSD following exposure to psychological trauma (de Vries & Olff, 2009; Reese et al., 2012). Twin studies proved that combat exposure is linked to PTSD, with the risk of developing PTSD increased by about ninefold in twins exposed to high combat compared with their noncombat-exposed twin brothers (Eisen, Neuman, Goldberg, Rice, & True, 1989; Goldberg, True, Eisen, Henderson, & Robinette, 1987; Goldberg et al., 1990; Henderson et al., 1990). Genetic factors account for 13–34% of the risk for the development of PTSD (Goldberg et al., 1990; True et al., 1993). Other studies demonstrated a genetic contribution to the risk of being exposed to traumatic stressors (Kendler, Thornton, & Gardner, 2000). One interpretation of this interesting finding is that certain inherited personality traits may determine who will walk point in a combat unit in Vietnam. Another view would be that certain families are walking disasters. For instance the family that due to alcoholism and family abuse and violence has a low socioeconomic status that causes them to live in a trailer in a rural area. That in turn exposes them to increased risks from natural disasters like hurricanes. The cycle of trauma keeps these family members trapped in a pattern of high risk. Overall, these studies demonstrated that a combination of genetic and environmental factors is responsible for the development of PTSD.

Other research looked at neurocognitive factors that could influence the risk for development of PTSD after exposure to psychological trauma. Some researchers have found pre-trauma exposure intelligence to increase the risk of PTSD (Macklin et al., 1998; McNally & Shin, 1995) while other studies found smaller hippocampal volume pretrauma predicted risk for PTSD (Gilbertson et al., 2002).

Genetic studies have examined the role of genes encoding various neuroreceptors in the risk of PTSD. Several studies have looked at the role of genes coding for the serotonin transporter, which controls reuptake of serotonin in the neuron, and is the target for the Selective Serotonin Reuptake Inhibitors (SSRIs). The genotype for the serotonin transporter (5HTTLPR) includes both S (short) and L (long) allele types. Genetic polymorphisms for the short form of the serotonin transporter were associated with increased risk for depression after stress exposure (Caspi et al., 2003). Studies in PTSD showed genes coding for the serotonin transporter and other serotonin receptors increased the risk (Kuzelova, Ptacek, & Macek, 2010; Pietrzak, Galea, Southwick, & Gelernter, 2012) including the short form of the serotonin transporter (Kenna et al., 2012; Koenen, Amstadter, & Nugent, 2009; Kuzelova et al., 2010; Lee et al., 2005; Wang et al., 2011). Other studies showed that that the serotonin transporter short form was associated with development of PTSD after natural disaster (Pietrzak et al., 2012) or exposure to childhood adversity (Xie et al., 2009). The L-S and G-A alleles of the serotonin transporter were examined, and the L (A) genotype was found to increase risk for PTSD (Grabe et al., 2009). The serotonin 5-HT_{2A} receptor is a postsynaptic receptor involves in regulation of behavior and other functions. The G allele was associated with an increased risk for PTSD in a sample of African-Americans (Mellman et al., 2009). Other studies showed positive response to selective serotonin reuptake inhibitor (SSRI) antidepressants with the LL allele of the serotonin transporter gene, and poor response in patients with the SS allele (Kenna et al., 2012; Mushtaq, Ali, Margoob, Murtaza, & Andrade, 2012), which was also associated with lack of response to cognitive-behavioral therapy (Bryant et al., 2010).

Studies have also looked at genes coding for the receptors and neurohormones in the HPA axis. A gene coding for the cortisol receptor, FKBB5, predicted the development of depression and response to treatment (Binder et al., 2005). Genes coding for corticotropin releasing factor (CRF) (Bradley et al., 2008) also predicted the development of depression.

In summary, these studies show that a combination of genetics, including patterns of physiological responses to stress, and the environment, via exposure to psychological trauma, play a role in the risk for PTSD following trauma (Kendler et al., 2000; Pitman, 2001).

Using the multilevel analysis approach we can combine all of these various factors to understand the effects of stress on the individual, including genetics, risk factors, neurobiology, personality, cultural, philosophical, and other factors.

THE INTERACTION OF DEVELOPMENTAL EPOCH AND THE BRAIN

One of the factors that need to be assessed in the multilayer assessment approach is the interaction between developmental epoch, brain development, and trauma. The age of the child and the level of brain development at the time of the trauma plays a critical role in determining long term outcomes. To understand this important variable we need to have an understanding of normal brain development, which we do here.

During the first 5 years of life there is an increase in both gray matter and white matter, which causes a general enlargement of the brain. Ongoing myelination results in an increase in white matter from age 5 to 18, while there is a decrease in gray matter secondary to neuronal pruning with no change in total brain size (Casey, Giedd, & Thomas, 2000; Durston et al., 2001; Giedd, Blumenthal, Jeffries, et al., 1999; Paus et al., 1999). The frontal and parietal cortex increase in volume during this time (Rapoport et al., 1999; Sowell et al., 1999) as do corpus callosum (Giedd, Blumenthal, & Jeffries, 1999; Thompson et al., 2000), hippocampus and amygdala (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Giedd, Vaituzis, et al., 1996; Pfefferbaum et al., 1994) while there is a decrease in volume of the basal ganglia (Giedd, Blumenthal, & Jeffries, 1999; Thompson et al., 2000). In mid childhood lateral ventricular size increases in size for boys (but not girls), while caudate and putamen size decreases in boys, but not girls (Giedd, Snell, et al., 1996). After the age of about 18–21 there is little change in the brain until very late in life, in the absence of pathological conditions like arteriosclerosis or Alzheimer's disease.

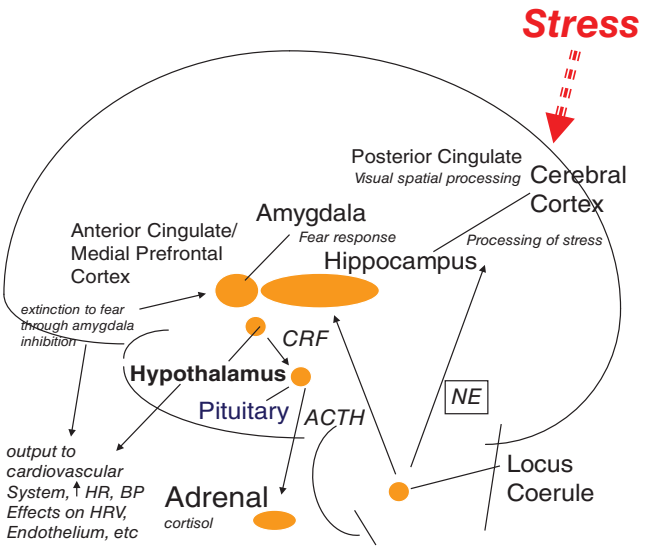


Figure 9.1 Model of how traumatic stress affects the brain. Stress is associated with acute increases in cortisol and norepinephrine. With chronic stress there is dysregulation of these systems with increased amygdala function and decreased hippocampal and medial prefrontal function. Outputs through the hypothalamus and medial prefrontal cortex increase peripheral sympathetic and cortisol function, increasing the risk of heart disease. See footnote 1.

BIOLOGICAL RESPONSES TO TRAUMA

Another variable in the multilevel assessment of trauma is the neurobiological response to trauma. Neuroscience has been touched on previously in this chapter but here we provide a more in depth view.

Trauma can have long-term effects on the body and physiological systems (Figure 9.1). Stress circuits like the cortisol and norepinephrine systems, and brain regions involved in memory, including the hippocampus, amygdala, and prefrontal cortex, are sensitive to stress (Bremner, 2002b; Bremner & Vermetten, 2001). These circuits and systems underlie symptoms of posttraumatic stress disorder (PTSD) and other stress-related mental disorders (Bremner, 2002a).

The hypothalamic-pituitary-adrenal (HPA) axis is activated by stress. Corticotropin-releasing factor (CRF) is released from the hypothalamus, with stimulation of adrenocorticotropin hormone (ACTH) release from the pituitary resulting in turn in cortisol release from the adrenal. CRF also acts centrally to create fear-related behaviors and triggers other neurochemical responses to stress, including the noradrenergic neurotransmitter system (Melia & Duman, 1991). Early life stress leads to long term sensitization of the HPA axis and CRF to further stressors (Coplan et al., 1996; Levine, Weiner, & Coe, 1993; Makino, Smith, & Gold, 1995; Plotsky & Meaney, 1993; Stanton, Gutierrez, & Levine, 1988). Stress also leads to over activation of the norepinephrine system, which plays a critical role in the fight-or-flight response (Bremner, Krystal, Southwick, & Charney, 1996a, 1996b).

A network of brain areas involved in memory and fear, including the hippocampus, medial prefrontal cortex, and amygdala, are involved in the brain's response to stress (Bremner, 2005b, 2011; Rauch, Shin, & Phelps, 2006). The hippocampus plays a critical role in memory and is also sensitive to stress. Studies in animals showed that stress resulted in damage to neurons in the CA3 region of the hippocampus (Gould, Tanapat, McEwen, Flugge, & Fuchs, 1998; Magarinos, McEwen, Flugge, & Fluchs, 1996; McEwen et al., 1992; Nibuya, Morinobu, & Duman, 1995; Sapolsky, 1996; Sapolsky, Uno, Rebert, & Finch, 1990). High levels of glucocorticoids seen with stress were also associated with deficits in new learning (Diamond, Fleshner, Ingersoll, & Rose, 1996; Luine, Villages, Martinex, & McEwen, 1994).

Brain-derived neurotrophic factor (BDNF) is a neuropeptide found in the hippocampus and other brain regions that has a trophic effect on neurons. Stress resulted in a reduction in brain-derived neurotrophic factor (BDNF) mRNA; CRF also had a direct effect

on the hippocampus in early development (Brunson, Eghbal-Ahmadi, Bender, Chen, & Baram, 2001). Antidepressant drugs, some anticonvulsants, and electroconvulsive therapy had the opposite effect on BDNF levels in the hippocampus (Malberg, Eisch, Nestler, & Duman, 2000; Nibuya et al., 1995; Watanabe, Gould, Cameron, Daniels, & McEwen, 1992).

Changes in the environment can also have an effect on the hippocampus, a finding that has implications for children growing up in abusive or neglectful families. Social enrichment increases hippocampal neurogenesis (Kempermann, Kuhn, & Gage, 1998). Maternal behavior influences glucocorticoid receptors in the hippocampus, an effect that can persist into adulthood (Liu, Diorio, Day, Francis, & Meaney, 2000; Meaney, Aitken, van Berkel, Bhatnager, & Sapolsky, 1988).

The medial prefrontal cortex also plays an important role in the stress response. This brain structure includes the anterior cingulate, orbitofrontal cortex, and adjacent areas. The mesofrontal dopamine system is involved in emotional responses and coping, and stress results in dopamine release in the medial prefrontal cortex (Arnsten, 2000; Deutch & Roth, 1990; Devinsky, Morrell, & Vogt, 1995; Pani, Porcella, & Gessa, 2000). The frontal cortex also inhibits function of the amygdala, a brain area involved in fear learning responses. This circuitry underlies extinction of fear responses (Milad & Quirk, 2002; Quirk, Garcia, & Gonzalez-Lima, 2006). Peripheral neurohormonal responses to stress are also regulated by the frontal cortex via relay stations in the spinal cord (Diorio, Viau, & Meaney, 1993; Feldman, Conforti, & Weidenfeld, 1995; Frysztak & Neafsey, 1994). This brain area is also sensitive to early stress, which leads to decreased branching of neurons (Radley et al., 2004).

Although understanding the interaction between childhood development, trauma, and physiology is critical, research in children is complicated by multiple factors. These include issues related to psychiatric diagnoses in children, reliability in assessment of trauma and symptoms, and informed consent (Cicchetti & Walker, 2001; Saigh, Yasik, Sack, & Koplewicz, 1990). Sexually abused girls were found to have normal baseline cortisol and blunted ACTH response to CRF (M.D. DeBellis, Chrousos, et al., 1994). Traumatized children with PTSD had increased levels of cortisol measured in 24-hour urines (DeBellis, Baum, et al., 1999). Emotionally neglected children from a Romanian orphanage had elevated cortisol levels over a diurnal period compared with controls (Gunnar, Morison, Chisolm, & Schuder, 2001). Elevated cortisol was also seen in children with clinical-level internalizing problems (Cicchetti & Rogosch, 2001). Depressed preschool children showed increased cortisol response to separation stress (Luby et al., 2003). Children with depression and abuse had an increased ACTH response to CRF challenge compared with children with depression without abuse (Kaufman et al., 1997).

The effects of early life trauma can result in neurobiological changes extending into adulthood (Cicchetti & Rogosch, 2001; Shea, Walsh, MacMillan, & Steiner, 2004). Women with childhood sexual abuse-related PTSD assessed with the Early Trauma Inventory (ETI), a reliable and valid measure of early abuse (Bremner, Bolus, & Mayer, 2007; J. D. Bremner, Vermetten, & Mazure, 2000) had decreased baseline cortisol based on 24-hour diurnal assessments of plasma with 10-minute sampling periods, a flattening of the normal diurnal cortisol curve, and increased pulsatility of cortisol reflecting dysregulation of CRF release, compared with women with abuse without PTSD, and women without abuse or PTSD (Bremner, Vermetten, & Kelley, 2007). Lower baseline cortisol was correlated with increased symptoms of PTSD in the PTSD group (Bremner et al., 2007). The normal cortisol rise after awakening has also has been shown to be blunted in PTSD patients (de Kloet, Vermetten, Heijnen, et al., 2007; Neylan et al., 2005; Wessa, Rohleder, Kirschbaum, & Flor, 2006), while pre-deployment cortisol response to awakening was not predictive of the development of PTSD (van Zuiden, Kavelaars, et al., 2011). Women with PTSD had increased cortisol responses in response to hearing personalized scripts of their childhood abuse (Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, 2003). Childhood abuse-related PTSD was also associated with increased cortisol response to cognitive stressors (Bremner, Vythilingam, Vermetten, Adil, et al., 2003). Combat veterans with PTSD assessed with 24-hour sampling showed lower plasma cortisol levels and a flattening of the normal diurnal curve (Yehuda, Teicher, Levengood, Trestman, & Siever, 1994). Measurement of cortisol in 24-hour urine collections show either normal or low cortisol in PTSD (Yehuda et al., 1995; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996) and increased suppression of cortisol to dexamethasone, reflecting increased sensitivity (Stein, Yehuda, Koverola, & Hanna, 1997; Yehuda, Halligan, Grossman, Golier, & Wong, 2002). Women with depression and a history of childhood abuse had increased cortisol response to a stressful cognitive challenge relative to controls (Heim et al., 2000) and a blunted ACTH response to CRF challenge (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001).

Changes in glucocorticoid receptor (GR) function are seen in PTSD (Vermetten, 2008). Cortisol regulates glucocorticoid receptors in the pituitary and hypothalamus providing feedback to the HPA axis. A proxy of glucocorticoid function can be measured indirectly by assessing cortisol levels following administration of glucocorticoids (e.g., dexamethasone) or through measurement of receptors in lymphocytes. PTSD is associated with increased suppression of cortisol with low dose (0.5 mg) dexamethasone, suggesting increased sensitivity of glucocorticoid receptors (Goenjian et al., 1996; Stein, Yehuda, et al., 1997; Yehuda & Boisoneau, 1995; Yehuda et al., 1993), although one study found this effect in traumatized non-PTSD subjects as well (de Kloet, Vermetten, Heijnen, et al., 2007). Other studies in PTSD showed increased glucocorticoid receptors in peripheral lymphocytes (Yehuda, Lowry, Southwick, Mason, & Giller, 1991) and hypersensitivity of pituitary response to metyrapone (Yehuda, Levengood, et al., 1996) (although see (Kanter et al., 2001), consistent with increased feedback sensitivity in PTSD. Elevations of glucocorticoid receptors were shown to be predictive of the development of PTSD after combat deployment (van Zuiden, Geuze, et al., 2011). PTSD was associated with a blunted effect of glucocorticoids (dexamethasone) on declarative memory function, suggesting decreased sensitivity of glucocorticoid receptors in the hippocampus (J. D. Bremner, Vythilingam, Vermetten, Newcomer, & Charney, 2004). One study showed a decrease, however, in GR in leukocytes in both traumatized PTSD and non-PTSD subjects in comparison to healthy controls, and a blunted suppression response of T-cell proliferation in leukocytes to dexamethasone that was specific to PTSD (de Kloet, Vermetten, Bikker, et al., 2007).

PTSD is associated with increases in corticotropin releasing factor (CRF). Male patients with combat-related PTSD had increased concentrations of CRF in the cerebrospinal fluid (CSF; Baker et al., 2005, 1999; Bremner, Licinio, et al., 1997; Sautter et al., 2003) and plasma (de Kloet et al., 2008). A study of civilian PTSD with low levels of comorbid psychiatric diagnoses found no difference in CSF CRF from controls (Bonne et al., 2011). PTSD was associated with a blunted ACTH response to CRF challenge, suggesting decreased pituitary sensitivity to CRF (Smith et al., 1989). No difference between PTSD patients and controls was found in ACTH or cortisol after administration of dexamethasone followed by a CRF challenge (de Kloet et al., 2008).

Increased noradrenergic and peripheral sympathetic function is associated with PTSD (Bremner, Krystal, et al., 1996a, 1996b). Symptoms characteristic of increased noradrenergic function include irritability, increased startle, hyperarousal, and sleep disturbance (Bremner, Krystal, et al., 1996b). Increased baseline concentrations of norepinephrine and its metabolites were found in patients with PTSD (DeBellis, Baum, et al., 1999; DeBellis, Lefter, Trickett, & Putnam, 1994; Lemieux & Coe, 1995; Mason, Giller, & Kosten, 1988; Yehuda, Siever, & Teicher, 1998), although some studies showed no baseline differences (Blanchard, Kolb, Prins, Gates, & McCoy, 1991; McFall, Veith, & Murburg, 1992; Mellman, Kumar, Kulick-Bell, Kumar, & Nolan, 1995; R.K. Pitman & Orr, 1990; Southwick et al., 1993). Increased concentrations of baseline norepinephrine and its metabolites were also found in cerebrospinal fluid of PTSD patients (Geracioti et al., 2001). Reminders of the original trauma in the form of pictures and sounds or scripts resulted in increased noradrenergic reactivity, shown by an increase in heart rate, blood pressure, and skin conductance, all markers of sympathetic function (Blanchard, Kolb, Gerardi, Ryan, & Pallmeyer, 1986; Blanchard, Kolb, Pallmeyer, & Gerardi, 1982; Bremner, Krystal, et al., 1996b; Malloy, Fairbank, & Keane, 1983; McFall, Murburg, Ko, & Veith, 1990; Orr, Lasko, Shalev, & Pitman, 1995; Orr, Pitman, Lasko, & Herz, 1993; Orr & Roth, 2000; Orr et al., 1998), as well as increased norepinephrine and epinephrine in plasma (Blanchard et al., 1991; McFall et al., 1992). Increased baseline heart rate after trauma exposure predicted subsequent development of chronic PTSD (Shalev, Sahar, Freedman, & et al., 1998).

Other indications of altered noradrenergic function in PTSD include decreased binding to platelet alpha$_2$ receptors (Perry, Southwick, & Giller, 1991), decreased activity of the second messenger, cyclic adenosine monophosphate (cAMP; Lerer, Bennet, Ebstein, Balkin, 1990; Lerer, Ebstein, Shestatsky, Shemesh, & Greenberg, 1987), and decreased platelet monoamine oxidase activity (Davidson, Lipper, Kilts, Mahorney, & Hammett, 1985). These findings suggest chronic increases in norepinephrine leading to compensatory changes in receptors and messenger systems related to noradrenergic function. Administration of the alpha$_2$ adrenergic receptor, yohimbine, which increases firing of noradrenergic neurons in the locus coeruleus, increased PTSD symptoms and anxiety, as well plasma concentrations of the norepinephrine metabolite, 3-Methoxy-4-hydroxyphenylglycol (MHPG) (Southwick et al., 1993, 1997). PTSD patients had a decrease in brain function in the medial prefrontal cortex with yohimbine not seen in healthy controls (decreased frontal lobe function occurs with excessive release of norepinephrine in that

brain area; Bremner, Innis, et al., 1997). These findings all support increased noradrenergic function in PTSD.

Patients with PTSD have smaller volume of the hippocampus as measured with magnetic resonance imaging (MRI), and deficits in declarative memory function, consistent with animal studies (Bremner, 2005b). Studies in children with PTSD from a variety of traumas have shown deficits in verbal memory and verbal IQ (Moradi, Doost, Taghavi, Yule, & Dalgleish, 1999; Saigh, Yasik, Oberfield, Halamandaris, & Bremner, 2006; Saltzman, Weems, & Carrion, 2006). Bremner et al. (Bremner, Randall, Capelli, et al., 1995) found deficits in verbal declarative memory as measured by the Wechsler Memory Scale (WMS), the verbal Selective Reminding Test (vSRT), and other measures, in male and female adults with childhood physical or sexual abuse related PTSD compared controls. Deficits in verbal memory in the childhood abuse patients were significantly correlated with severity of childhood sexual abuse. One study in adult women with sexual abuse-related PTSD showed deficits in verbal declarative memory compared with both women with abuse without PTSD and nonabused non-PTSD women (Bremner, Vermetten, Nafzal, & Vythilingam, 2004). Another study in women with early childhood sexual abuse in which some, but not all, of the patients had PTSD, showed no difference between abused and nonabused women (Stein, Hanna, Vaerum, & Koverola, 1999). These studies suggest that early abuse with associated PTSD results in deficits in verbal declarative memory. Women with childhood abuse-related PTSD also show cognitive impairments as evidenced by an increase in false recall of critical lures on a memory test involving recall from a list of highly semantically related words (Bremner, Shobe, & Kihlstrom, 2000; Clancy, Schacter, McNally, & Pitman, 2000).

Studies have also consistently shown smaller hippocampal volume in both male and female adults with PTSD related to a range of traumas, including childhood abuse (Bremner, 2006; Karl et al., 2006; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Smith, 2005). A study of women with early sexual abuse, most of whom met criteria for PTSD, showed smaller hippocampal volume compared with nonabused women (Stein, Koverola, Hanna, Torchia, & McClarty, 1997). Women with early childhood sexual abuse and PTSD had smaller hippocampal volume compared with both abused women without PTSD, and nonabused non-PTSD women (Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer, et al., 2003). Another study showed smaller hippocampal volume in adult women with PTSD only in those who were abused at specific periods in early childhood (Andersen et al., 2008). Other studies in PTSD have found smaller hippocampal volume and/or reductions in NAA, a marker of neuronal integrity (Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer, et al., 2003; Emdad et al., 2006; Freeman, Cardwell, Karson, & Komoroski, 1998; Gilbertson et al., 2002; Hedges et al., 2003; Irle et al., 2005; Li et al., 2006; Lindauer, Olff, van Meijel, Carlier, & Gersons, 2006; Lindauer, Vlieger, et al., 2004; Lindauer et al., 2005;

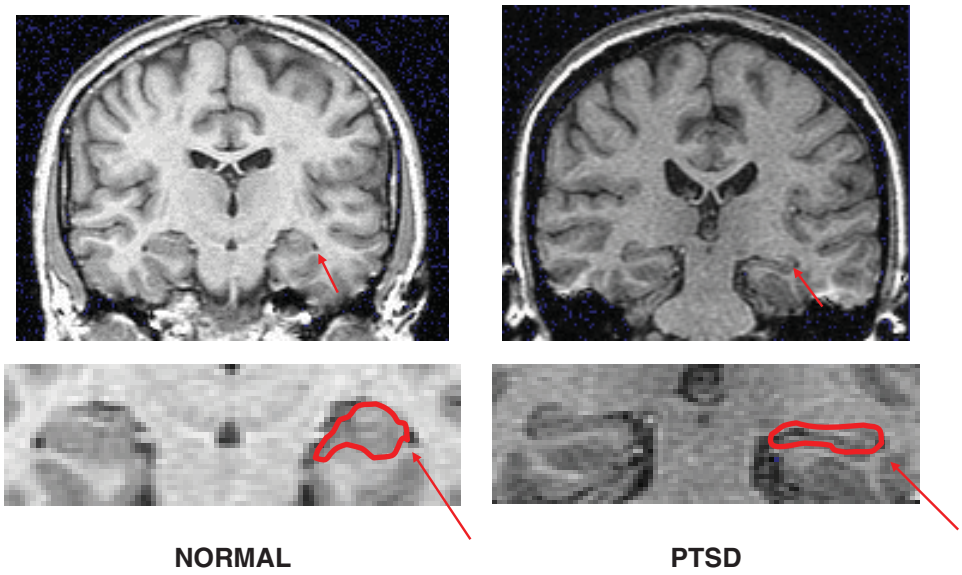


Figure 9.2 Hippocampal volume in PTSD on a coronal MRI. The hippocampus is visibly smaller in the PTSD patient compared with a normal control. See footnote 1.

Mahmutyazicioglu et al., 2005; Schuff et al., 2001; Shin, Shin, et al., 2004; Villarreal et al., 2002).

Studies of children with abuse-related PTSD have not shown smaller hippocampal volume (Carrion et al., 2001; DeBellis, Hall, Boring, Frustaci, & Moritz, 2001; DeBellis, Keshavan, et al., 1999), although one study showed a correlation between cortisol and reduction in hippocampal volume over time (Carrion, Weems, & Reiss, 2007). Meta-analyses show that smaller hippocampal volume is seen to an equal degree in both men and women with PTSD, related to both childhood abuse and adult traumas like combat, and in both left and right hippocampi (Kitayama et al., 2005; Smith, 2005). Findings of smaller hippocampal volume in adults with childhood abuse-related PTSD, but not in abused children, suggests a delayed effect of abuse on the brain, consistent with findings from animal studies (Brunson et al., 2005).

PTSD is also associated with deficits in hippocampal function. Women with childhood sexual abuse-related PTSD had deficits in hippocampal activation while performing a verbal declarative memory task as measured with brain imaging compared with non-PTSD women (Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer, et al., 2003). A reversal of hippocampal atrophy and hippocampal-based memory deficits was seen with treatment with the SSRI, paroxetine (Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003). Hippocampal dysfunction may memory dysregulation in PTSD, including increased fear learning, deficits in explicit memory deficits and fragmentation of memory in abuse survivors (Bremner, 2005b).

Alterations in the frontal cortex and other brain structures are associated with PTSD. Women with childhood abuse-related PTSD had smaller anterior cingulate volume as measured with MRI compared with controls (Kitayama et al., 2005), while other studies showed smaller anterior cingulate volumes in women with PTSD (Shin et al., 2009) as well as smaller frontal lobe volumes (Andersen et al., 2008). Reduced NAA (indicating loss of neuronal integrity) was found in medial prefrontal cortex in boys and girls with childhood PTSD (M.D. DeBellis, Keshavan, Spencer, & Hall, 2000). Other findings include smaller volume of the corpus callosum in women with childhood abuse-related PTSD (Andersen et al., 2008; Kitayama et al., 2007). In children with PTSD, boys showed greater reduction in corpus callosum and greater ventricular volumes than girls (DeBellis & Keshavan, 2003). In summary, these studies show structural alterations in the hippocampus and frontal cortex in PTSD (Bremner, 2011; Bremner & Vermetten, 2012).

THE NEURAL CIRCUITRY OF PTSD

A network of brain regions including the medial prefrontal cortex, amygdala, and hippocampus, are involved in mediating the symptoms of PTSD (Bremner, 2010). Girls with a history of poor emotional response to maltreatment had a relative decrease in left versus right frontal lobe activity as measured by electroencephalogram (EEG; Curtis & Cicchetti, 2007). Other studies showed alterations in EEG measures of brain activity in the frontal cortex and left hemisphere of traumatized children (Ito et al., 1993; Miskovic, Schmidt, Georgiades, Boyle, & MacMillan, 2010; Schiffer, Teicher, & Papanicolaou, 1995).

Brain imaging studies also show abnormalities in these areas in adults with PTSD (Bremner, 2011) (see Figure 9.3). Exposure to memories of childhood sexual abuse with personalized traumatic scripts in women with childhood sexual abuse-related PTSD resulted in decreased blood flow in the medial prefrontal cortex/anterior cingulate, including Brodmann's area 25, or subcallosal gyrus, and area 32, as well as decreased blood flow in parietal cortex and inferior frontal gyrus (Bremner, Narayan, et al., 1999; Shin et al., 1999) (see Figure 9.5), hippocampus and visual association cortex (Bremner, Narayan, et al., 1999). Retrieval of emotionally valenced words (Bremner et al., 2001; e.g., rape-mutilate) in women with PTSD from early abuse resulted in decreases in blood flow in the medial prefrontal cortex (Brodmann's areas 25, 32, 9), left hippocampus, and fusiform gyrus/inferior temporal gyrus, with increased activation in posterior cingulate, left inferior parietal cortex, left middle frontal gyrus, and visual association and motor cortex (Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Staib, et al., 2003). Decreased medial prefrontal cortical/anterior cingulate activation, and decreased visual association and parietal cortex function, was seen in women with abuse-related PTSD during performance of the emotional Stroop task (i.e., naming the color of a word such as rape; Bremner, Vermetten, Vythilingam, et al., 2004). A number of studies have replicated the finding of decreased medial prefrontal cortex function during exposure to traumatic reminders in the form of traumatic slides and/or sounds or traumatic scripts using PET, SPECT, or fMRI (Bremner, Narayan, et al., 1999; Bremner, Staib, et al., 1999; Britton, Phan, Taylor, Fig, & Liberzon, 2005; Lanius et al., 2001; Lanius et al., 2003; Liberzon et al., 1999; Lindauer, Booij, et al., 2004; Phan, Britton, Taylor, Fig, & Liberzon, 2006; Semple et al., 2000; Shin, Orr, et al., 2004; Shin et al., 1997, 1999, 2001, 2005; Yang, Wu, Hsu, & Ker, 2004).

Studies showed increased amygdala function in PTSD. Women with childhood sexual abuse-related PTSD had

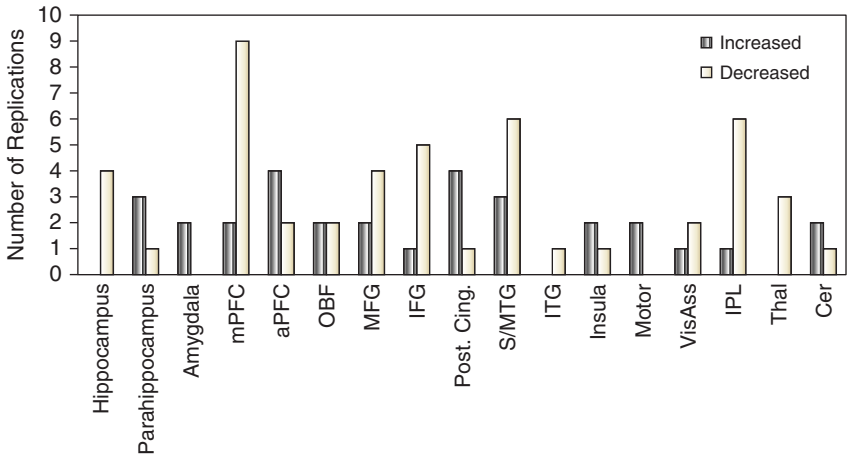


Figure 9.3 Replicated findings in PTSD. The most replicated findings related to symptom provocation are decreased medial prefrontal function. Other findings include decreased hippocampal and dorsolateral prefrontal function and increased amygdala function. See footnote 1.

increased amygdala activation with classical fear conditioning, and decreased medial prefrontal cortex function with extinction, compared with healthy nonabused women (Bremner et al., 2005; Figure 9.4). Increased amygdala function and decreased medial prefrontal function was seen with traumatic reminders (Shin, Orr, et al., 2004), indicating a failure of inhibition of the amygdala by the medial prefrontal cortex could account for increased PTSD symptoms with traumatic reminders. Other studies found increased amygdala and parahippocampal function and decreased medial prefrontal function during performance of an attention task (Semple et al., 2000), and increased amygdala function at rest (Chung et al., 2006), during a working memory task (Bryant et al., 2005), during recall of traumatic words (Protopopescu et al., 2005), with exposure to masked fearful faces (Armony, Corbo, Clement, & Brunet, 2005; Rauch et al., 2000), overt fearful faces (Shin et al., 2005), traumatic sounds (Liberzon et al., 1999; Pissiota et al., 2002), traumatic scripts (Rauch et al., 1996), or trauma-related smells (diesel in veterans; Vermetten, Schmahl, Southwick, & Bremner, 2007).

Other findings in studies of traumatic reminder exposure include decreased function with exposure to traumatic reminders in hippocampus (Bremner, Narayan, et al., 1999), thalamus (Lanius et al., 2001; Lanius et al., 2003), visual association cortex (Bremner, Narayan, et al., 1999; Lanius et al., 2003; Shin et al., 1997; Shin, Orr, et al., 2004), parietal cortex (Bremner, Narayan, et al., 1999; Rauch et al., 1996; Sakamoto et al., 2005; Shin et al., 1997; Shin et al., 1999), and inferior frontal gyrus (Bremner, Narayan, et al., 1999; Lanius et al., 2003; Rauch et al., 1996; Sakamoto et al., 2005; Shin et al., 1997; Shin et al., 1999; Shin et al., 2001), and increased function in posterior cingulate (Bremner, Narayan, et al., 1999; Bremner, Staib, et al., 1999; Lanius et al., 2001; Shin et al., 1997), insula (Vermetten et al., 2007), and parahippocampal gyrus (Bremner, Narayan, et al., 1999; Bremner, Staib, et al., 1999; Liberzon et al., 1999).

PET and SPECT studies of neuroreceptors in PTSD showed reduced binding of benzodiazepine receptors in the brain in combat veterans in the frontal cortex in some studies (Bremner, Innis, et al., 2000; Geuze et al., 2008) but not others (Fujita et al., 2004). One study found no changes in binding of the 5HT1A serotonin receptor in PTSD (Bonne et al., 2005). Other studies found a reduction in anterior cingulate opiate receptor binding (Liberzon et al., 2007) and an increase in hippocampal beta2 nicotinic acetylcholine receptor binding in PTSD (Czermak et al., 2008).

As mentioned already, the trauma-spectrum model of stress-related mental disorders (Bremner, 2002a) was tested by assessing similarities in neurobiology. We hypothesized that these disorders would have similar abnormalities in specific brain areas, including the amygdala, medial prefrontal cortex, and hippocampus. As mentioned above, these disorders include abuse-related PTSD, depression associated with early abuse, borderline personality disorder (BPD) associated with early abuse, and dissociative identity disorder (DID) with early abuse. Women with a history of childhood trauma with and without the diagnosis of BPD were exposed to the stress of a script outlining a personally upsetting abandonment scene in conjunction with PET imaging of the brain (Schmahl, Elzinga, et al., 2003). As predicted, women with BPD had

decreased function in the medial prefrontal cortex. They did not have similar responses to scripts of childhood abuse, unlike women with PTSD (Schmahl, Vermetten, et al., 2004a). Women with BPD and abuse had increased psychophysiological responses to abandonment scripts relative to trauma scripts, while women with PTSD and abuse had the opposite pattern (Schmahl, Elzinga, & Bremner, 2002). This showed differential responses in these two disorders in spite of the common exposure to early abuse. Studies of structural MRI showed smaller hippocampal volume across several trauma spectrum disorders, including abuse-related PTSD (Bremner, Randall, et al., 1997; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer, et al., 2003), DID with early abuse (Vermetten et al., 2006), BPD with early abuse (Driessen et al., 2000; Schmahl, Vermetten, et al., 2003), and depression with early abuse (Vythilingam et al., 2002). Patients with another anxiety disorder, panic disorder, did not show a reduction in hippocampal volume (Vythilingam et al., 2000).

Patients with trauma spectrum disorders exhibit other alterations in stress responsive neurohormonal systems. HPA axis dysfunction, and a functional dysregulation of the prefrontal-limbic axis, are seen in BPD that are similar to PTSD (Donegan et al., 2003; Driessen et al., 2004; Juengling et al., 2003; Lange et al., 2005; Schmahl & Bremner, 2006; Schmahl, Elzinga, et al., 2003; Schmahl, McGlashan, et al., 2002; Schmahl, Vermetten, et al., 2004a; Schmahl, Vermetten, et al., 2004b). There are also important differences in physiological reactivity between BPD and PTSD patients, even in groups where all subjects were exposed to childhood sexual abuse. BPD subjects respond to reminders (scripts) of abandonment but not traumatic memories, and PTSD subjects having the opposite response (Schmahl, Elzinga, et al., 2004). These findings are consistent with a common neurobiology and neurocircuitry underlying the trauma-spectrum disorders, including PTSD, DID, BPD, and depression related to early abuse, as well as some differences. The partial overlap of neurobiology then parallels the partial overlap in symptomatology in patients with trauma-related mental disorders.

EFFECTS OF TRAUMA ON THE BODY

The multiple levels of analysis approach include an examination of stress on physical health in addition to mental health. Traumatic stress has negative effects on several physical disorders especially when associated with diagnoses like PTSD and depression (Proctor, Harley, Wolfe, Heeren, & White, 2001; Proctor et al., 1998; Wagner, Wolfe, Rotnitsky, Proctor, & Erickson, 2000; Zatzick et al., 1997). PTSD is associated with an increased risk for heart disease, probably through multiple pathways including activation of neurohormonal or brain circuit pathways (Vaccarino & Bremner, 2011). Stress-induced activation of norepinephrine and cortisol or changes associated with chronic PTSD may lead to an increase in atherosclerosis or vulnerability to cardiac arrhythmias or other consequences that increase the risk for heart disease. Stress-induced mental disorders may lead to poor health outcomes directly, or through an increase in risk factors like smoking, lack of exercise, or obesity. For instance, childhood abuse is associated with an increase in smoking (Beckham, 1999; Butterfield, Forneris, Feldman, & Beckham, 2000; Dube et al., 2003), which leads to increased risk of cancer and heart disease. Childhood abuse is also associated with increased rates of substance abuse and obesity in adulthood (Dube et al., 2003; Williamson et al., 2002). Increased obesity leads to increased risk of both heart disease and diabetes, which is worsened by antipsychotic medications that are often used for the treatment of PTSD. A third possibility is that the same factors (e.g., genetic predisposition) that increase risk for physical disorders also increase risk for stress-induced mental disorders.

Heart disease is an important outcome from stress (Berkman, Vaccarino, & Seeman, 1993; Krumholz et al., 1998; Rozanski, Blumenthal, & Kaplan, 1999). Heart disease is increased in both depression (Carney & Freedland, 2003; Evans et al., 2005) and PTSD (Vaccarino et al., 2013). This is seen in depressed patients with (Barefoot, Helms, & Mark, 1996; Barth, Schumacher, & Herrmann-Lingen, 2004; Borowicz et al., 2002; Burg, Benedetto, Rosenberg, & Soufer, 2003; Carney, Rich, & Freedland, 1988; Carney et al., 2003; Connerney, Shapiro, McLaughlin, Bagiella, & Sloan, 2001; Frasure-Smith, Lesperance, Juneau, Talajic, & Bourassa, 1999; Frasure-Smith, Lesperance, & Talajic, 1993; Jenkins, Stanton, & Jono, 1994; Mallik et al., 2005; Mendes de Leon et al., 1998; Perski et al., 1998; Rutledge et al., 2006; van Melle et al., 2004) and without (Anda, Williamson, & Jones, 1993; Barefoot & Schroll, 1996; Carney & Freedland, 2003; de Jonge, van der Brink, Spijkerman, & Ormel, 2006; Ford et al., 1998; Fredman, Magaziner, Hebel, Hawkes, & Zimmerman, 1999; Hippisley-Cox, Fielding, & Pringle, 1998; Pratt et al., 1996) a prior history of heart disease (CHD).

Depression rates are higher in young women after myocardial infarction (MI, or heart attack) than other age and gender groups (Mallik et al., 2006), and depression

worsens outcomes in coronary artery disease (CAD) patients, whether symptoms are present at the time of the heart attack, or develop later (Parashar et al., 2006). Depression is also related to poor outcomes in congestive heart failure (CHF) patients (Vaccarino, Kasl, Abramson, & Krumholz, 2001).

Studies have shown that stress, which is linked to depression, can induce myocardial ischemia (decreased blood flow to the heart) in heart disease patients (Batten, Aslan, Maciejewski, & Mazure, 2004; Berkman et al., 1993; Boscarino, 1997; Brass & Page, 1996; Dong et al., 2004; Dube et al., 2003; Engel, Liu, McCarthy, Miller, & Ursano, 2000; Felitti et al., 1998; Joynt, Whellan, & O'Connor, 2003; Krumholz et al., 1998; Proctor et al., 2001; Proctor et al., 1998; Rosengren et al., 2004; Rozanski et al., 1999; Wagner et al., 2000; Williamson et al., 2002; Zatzick et al., 1997). Mental stressors can induce myocardial ischemia in certain vulnerable individuals on a daily basis (Arrighi et al., 2000; Arrighi, Burg, Cohen, & Soufer, 2003; Blumenthal et al., 1995; Burg, Jain, Soufer, Kerns, & Zaret, 1993; Soufer, 2004; Soufer et al., 1998; Stone et al., 1999) often occurring without pain in undiseased coronary arteries (possibly due to coronary vasospasm; Deanfield et al., 1984; Lacy et al., 1995), and often without the physical stress (e.g., exercise) that typically induces myocardial ischemia (Becker et al., 1996; Deanfield et al., 1984; Jain et al., 1998; Krantz et al., 1991; LaVeau et al., 1989; Ramachandruni et al., 2006; Rozanski et al., 1988; Schang & Pepine, 1977; Schiffer, Hartley, Schulman, & Abelmann, 1980). These studies showed that stress can induce painless myocardial ischemia that occurs with emotional activities and is not necessarily associated with emotion induced increased heart rate and blood pressure. Mental stress-induced ischemia, which can occur in normal vessels, is related to abnormal constriction of coronary arteries (Dakak, Quyyumi, Eisenhofer, Goldstein, & Cannon, 1995; Kop et al., 2001; Sherwood, Johnson, Blumenthal, & Hinderliter, 1999; Wittstein et al., 2005; Yeung et al., 1991) and may carry a greater risk than exertion related ischemia Mental stress-induced myocardial ischemia is associated with increased long-term risk for cardiac events that in many patients is more significant than exercise-induced myocardial ischemia (Goldberg et al., 1996; Jain, Burg, Soufer, & Zaret, 1995; Jiang et al., 1996; Krantz et al., 1999; Legault, Langer, & Armstong, 1995; Sheps et al., 2002). Psychological factors related to stress include the presence of strong emotions like anger (Boltwood, Taylor, Boutte Burke, Grogin, & Giacomini, 1993; M. M. Burg et al., 1993; Gabbay et al., 1996; Mittleman et al., 1995; Strike, Perkins-Porras, Whitehead, McEwan, & Steptoe, 2006; Strike & Steptoe, 2005). Anger and irritability, symptoms of PTSD, therefore contribute to increased risk of heart attacks.

Mental stress also causes a decrease in heart rate variability (the normal increase and decrease in heart rate that occurs with respiration (Lampert, Ickovics, Viscoli, Horwitz, & Lee, 1998) which increases the risk of sudden death from arrhythmia. Stress and emotion also have effects on myocardial electrical stability, increasing the risk for cardiac arrhythmias (Kop et al., 2004; Lampert et al., 2002; Lane et al., 2005).

Depression and PTSD, as noted above, could increase CHD risk through known associations with unhealthy behaviors, like lack of exercise, smoking, and poor diet, or through direct effects on the cardiovascular system (Hemingway & Marmot, 1999; Wulsin, Vaillant, & Wells, 1999). Stressful life events have been linked to the onset of episodes of major depression (Kendler et al., 2000) and stress could lead to both heart disease and depression and PTSD independently, it could mediate its effects through stress-related disorders, or vulnerability to both could be related to common factors. Stress is associated with increased cortisol and norepinephrine release, as well as increased heart rate and blood pressure (Bremner, Krystal, et al., 1996a, 1996b), which can impact negatively on cardiovascular function (Troxler, Sprague, Albanese, Fuchs, & Thompson, 1977). An excess in cortisol level may increase the risk for cardiovascular disease by injuring the intima (Kemper, Baggenstoss, & Slocumb, 1957; Nahas, Brunson, King, & Cavert, 1958) or by inducing inflammation in the artery wall (Gabay & Kushner, 1999; Musselman, Evans, & Nemeroff, 1998).

Both depression and PTSD are associated with elevations of sympathetic function, associated with increases in heart rate and blood pressure (Bremner, Krystal, et al., 1996a, 1996b; Delgado & Moreno, 2000). PTSD and depression related to childhood abuse, as discussed above, are also associated with increases in stress-induced cortisol release, especially related to specific traumatic reminders (Bremner, Vythilingam, Vermetten, Adil, et al., 2003; Elzinga et al., 2003; Heim et al., 2000). Stress-induced activation of norepinephrine may lead to damage to the endothelium, or inner lining of the coronary arteries, as well as accelerated atherosclerosis (Kaplan, Manuck, Adams, Weingand, & Clarkson, 1987; Kaplan, Manuck, Clarkson, Lusso, & Taub 1982; Troxler et al., 1977). An excess in cortisol levels with stress may also increase the risk for cardiovascular disease by injuring the endothelium (Kemper et al., 1957; Nahas et al., 1958).

Traumatic stress may also mediate its effects through brain areas sensitive to stress that are affected by PTSD and depression, including amygdala, medial prefrontal cortex, and hippocampus. These brain circuits have direct or indirect outputs through the hypothalamus and medial prefrontal cortex to neurohormonal systems (cortisol, norepinephrine) that influence heart function. The medial prefrontal cortex and anterior cingulate are unique in directly mediating cortisol and sympathetic responses to stress via the brainstem (Diorio et al., 1993). The hippocampus and medial prefrontal cortex have inhibitory pathways to the amygdala (Milad & Quirk, 2002; Morgan & LeDoux, 1995; Morgan, Romanski, & LeDoux, 1993; Phillips & LeDoux, 1992), which activates the stress response (Davis, 1992; Hitchcock & Davis, 1986; Hitchcock, Sananes, & Davis, 1989; LeDoux, 1993; Miserendino, Sananes, Melia, & Davis, 1990; Rosen & Davis, 1988), including activation of the peripheral stress response through pathways through the lateral hypothalamus which activate cortisol and sympathetic pathways in the periphery (Hitchcock & Davis, 1991).

Using the paradigm of inducing mental stress in the laboratory in conjunction with simultaneous heart and brain imaging, we have studied heart and brain correlates of stress in heart disease patients. These studies show that heart disease patients exposed to stress show involvement of the prefrontal cortex and other brain areas involved in the stress response (Soufer et al., 1998). In our studies we have patients undergo the stress of performing mental arithmetic or giving a stressful speech with negative feedback in conjunction with PET imaging of brain blood flow and injection of a radiopharmaceutical that takes a snapshot of heart blood flow. Subjects can then be moved to the SPECT camera for imaging of the heart. Using these techniques, we found that patients with a history of traumatic stress and depression had increased myocardial ischemia, typically experienced without chest pain, following stress as measured with cardiac SPECT (Bremner et al., 2009). Patients with depression and heart disease compared with heart disease patients without depression had decreased medial prefrontal responses during stress, with the greatest changes in those with stress-induced myocardial ischemia. Brain areas involved in stress and stress-related mental disorders were shown to be involved in the stress response in patients with stress-induced myocardial ischemia. Increased heart disease mortality in patients with PTSD or depression could be mediated through silent myocardial ischemia mediated by these brain pathways.

MULTIPLE LEVELS OF ANALYSIS

In this chapter we have reviewed the multilevel analysis approach as it applies to the study psychological trauma and its effects on the individual. We have advocated for the multilevel analysis approach as opposed to other approaches that look at the phenomenon from a unidimensional perspective, like the medical model of depression and PTSD. The multilevel analysis approach requires interdisciplinary team work, as it isn't possible for one person to have expertise in all of the areas involved, including psychology, psychiatry, psychotherapy, neurobiology, pharmacology, physical health, and general physiology, developmental psychology, sociology, and cultural aspects.

An example of the advantages of the multilevel analysis approach is in the field of heart disease. For years cardiologists focused on modifying the traditional risk factors

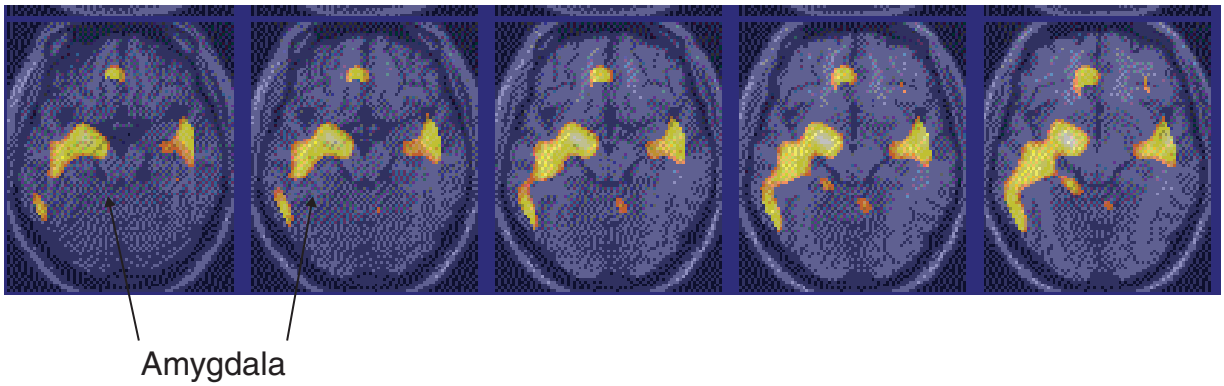


Figure 9.4 Amygdala function in PTSD. With classical fear conditioning (pairing of an unconditioned stimulus [shock] with conditioned stimulus [seeing a blue square on a screen] there was increased amygdala activation in PTSD relative to controls, suggesting increased sensitivity of the amygdala in the learning of fear. See footnote 1.

for heart disease, namely hypercholesterolemia, obesity, diabetes, and smoking. These factors, however, in total accounted for less than half of the risk for heart disease. The field was at an impasse until psychologists, psychiatrists, epidemiologists, and experts from other specialties got involved, and furthered research that demonstrated the important role of behavioral factors like stress and emotionally reactivity. Another problem with the pure medical model was that there was no recognition that early childhood abuse was independently associated with obesity and smoking. Therefore the relevant cause may be something different than it at first appears.

The single-level approach may limit the effectiveness of interventions. Rather than focus on smoking cessation programs, perhaps the individual needs psychotherapy or pharmacotherapy for PTSD. Once the PTSD symptoms are in control, it will not be as difficult to successfully stop smoking. This is just one example of how the multilevel analysis approach can improve treatment interventions and possibly outcomes.

Sometimes experts in different disciplines study the same things under different names. They may use a different language, or jargon, publishing in different journals, attending different meetings, and getting support from different sources. Cardiologists may be treating stress-related heart disease, while psychiatrists are dealing with PTSD patients suffering from chest pain or light-headedness. If these different disciplines can combine or join forces their collective effort will be superior to either acting alone. This was the impetus behind organizations like the National Institutes of Health or private foundations dedicated to supporting research and treatment for specific conditions to advocate for the breaking down of barriers or silos between different research groups and disciplines. It is also behind the new Veterans Administration practice of embedding psychiatrists in primary care clinics.

The multilevel analysis approach may be more complex or unfamiliar than the traditional single dimensional model. One cause, one treatment is simpler and easier to teach.

Research in the psychology field is typically based on self-report data. We rely on people to accurately and honestly report their symptoms. There is no objective or valid way of assessing mental disorders that does not involve the patient. People will arrive at similar points through different pathways; therefore, relying only on self-report data may not be useful or could even be misleading. The addition of other types of data, for instance, brain imaging results or genetic analyses, to the self-report data may provide a clearer picture of the disorder, which provides a

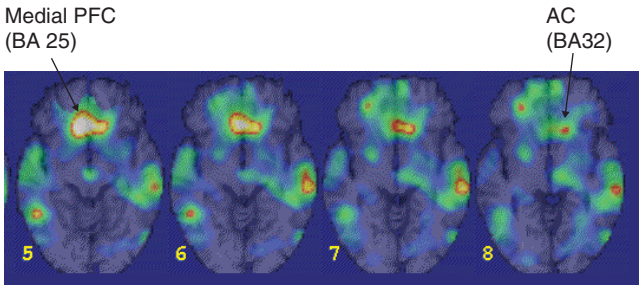


Figure 9.5 Effects of combat related slides and sounds on brain function. Outlined area shows decreased blood flow with combat slides in sounds in combat veterans with PTSD. This area normally inhibits the amygdala (involved in fear responses). See footnote 1.

view of the endophenotype (Kagan, Snidman, McManis, Woodward, & Hardway, 2002).

Neurobiology and psychology play off each other in important ways after a psychological trauma (Kopnisky, Cowan, & Hyman, 2002). Trauma can result in ruminative thinking that leads to a memory rehearsal effect. This may affect the formation of long-term traumatic memories that are indelible to intervention. Feelings of fear or upset with traumatic reminders results in enhanced cortisol and norepinephrine release, which in turn modulate memory storage (McGaugh, 2000). Brain areas involved in memory and the fear reaction including the hippocampus, amygdala, and prefrontal cortex further enforce the memory circuitry. Interventions like the teaching of mindfulness meditation may help patients break free from this cycle of ruminative memories and overconsolidation, with the long-term benefits for the patient (Bishop et al., 2004)

Biological research in the field of mental disorders also benefits from a multilevel analysis approach. For instance, there was originally the idea that a gene would be discovered for each of the psychiatric disorders, and that would correspond to an abnormality in a specific area of the brain as determined by brain imaging that would be different for each disorder. However, subsequent findings in genetics are more consistent with combinations of genes that may confer risk for multiple psychiatric disorders ranging from psychosis to attention deficit disorders. These disorders on the surface do not appear to be related. This is an illustration of multipotentiality. Alternatively, the equifinality model might state that bipolar disorder could be related to genetics in one individual, and childhood trauma in another. The two persons started out from different places but arrived at the same result. In a similar vein, as discussed already, brain imaging in the trauma spectrum disorders have discovered more similarities than differences, not consistent with the one disorder one brain lesion model. Researchers

are also forced to think in terms of functional circuits of brain regions that mediate symptoms of the disorder (Johnson, Halit, Grice, & Karmiloff-Smith, 2002).

Developmental psychopathology also benefits from the multilevel approach. Brain development interacts with environment and genetics in the formation and development of childhood mental disorders. Other factors are important, such as whether a child remains in an abusive home or ends up in foster care. Removal of the trauma will permit the process of healing to begin. Other children may grow out of their mental disorder. The effects of early trauma may not appear in the form of a mental disorder until later in life. This may be caused by a subsequent stressor that pushes the individual into a mental disorder, or the delayed effects of the primary trauma. Symptoms that appear one way at a specific developmental epoch may change in adulthood (Harrington, Rutter, & Fombonne, 1996). There may be the appearance of moving from one diagnosis to another as childhood transitions to adulthood (Harrington et al., 1996; Saigh et al., 2000).

Research on mediators and modulators that influence outcomes of the trauma response are also part of the framework of a multilevel analysis approach. Some individuals appear to be naturally resilient to the effects of psychological trauma (Bonanno, 2004). Social support (Keane et al., 1987), education level, older age (Brewin et al., 2000), and the absence of prior trauma (Bremner et al., 1993) positively affect long-term outcome. Prospective studies are needed to understand why some people develop chronic PTSD from psychological trauma and others don't. Applying the multilevel analysis approach to longitudinally collected data to assess responses at different stages of development and how they are influenced by individual, societal, cultural, economic, physical, and other factors will be useful.

TRANSLATIONAL IMPLICATIONS OF THE MULTILEVEL DEVELOPMENTAL PSYCHOPATHOLOGY PERSPECTIVE

The multilevel developmental psychopathology approach has many implications for transfer of knowledge in multiple areas to practical applications that are beneficial to individuals exposed to childhood trauma. This approach allows for the drawing of knowledge from multiple areas and is based on the idea that no one single discipline or body of knowledge is sufficient for the optimal approach to the individual with a history of childhood trauma. By way of example, studies have shown that the combination of psychotherapy and antidepressant medication is superior to either one alone in patients with a history of childhood abuse and major depression (Nemeroff et al., 2003).

Incorporating developmental psychology into the approach to childhood trauma survivors has a number of advantages. Taking into account the developmental epoch (or epochs) at which the trauma occurred and the stage of development permits a more specific application of diagnosis and intervention. The multilevel developmental psychopathology approach will likely be of more service to individuals affected by psychological trauma.

FUTURE DIRECTIONS

The use of the multilevel analysis approach to the study of the effects of psychological trauma on the individual has been reviewed in this chapter. Multilevel analysis involves looking at phenomena on multiple levels, including psychological, biological, cultural, genetic, physical, social, and political. For complex questions such as the effects of trauma on the individual it is important to analyze multiple variables simultaneously. These elements often cannot be separated. For example a change in a sense of meaning which results from exposure to psychological trauma may be driven by changes in neurotransmitters and brain circuits associated with the development of PTSD. Alternatively, the symptoms of PTSD can change an individual's perception of the world. The process of recovery involves psychological, spiritual, biological, and cultural factors. Changes in brain areas involved in memory and the regulation of behavior, like the hippocampus and medial prefrontal cortex, may have implications for issues such as school performance and delinquency that have ramifications on societal, cultural, and judicial levels as well. The cycle of violence of childhood abuse that crosses generations can be understood on a psychological or metaphorical level as well as a social and judicial level.

Future research should incorporate the multilevel analysis approach in the area of psychological trauma. This involves the avoidance of false dichotomies between mind, brain, and body. Treatments can incorporate elements of behavior, emotion, spirituality, biology, and cognition. Research studies need to incorporate in their designs multiple outcomes, with measures of behavior, spirituality, biology, health, and cognition, and follow patients longitudinally whenever possible. Research that goes beyond limits of defined and restricted disciplines or areas of expertise will help us to discover more effective treatments and to more successfully facilitate recovery in our patients.

CONCLUSIONS

This chapter reviewed the limitations of the single disorder, single treatment approach. It presents an argument for going beyond the single etiology, single disease, single treatment model, which has not led to consistent improvements on patient responses. Biological therapies have a role in the treatment of the traumatized patient, but other aspects need to be addressed as well. Meditation can add a sense of control and facilitate the recovery process (Astin, 1997; Weissbecker et al., 2002), providing a way for trauma victims to gain control of their thoughts and memories and become less emotionally reactive. The distressing memory is passively observed without efforts to control it, interrupting the pattern of ruminative thinking (Teasdale, Segal, & Williams, 1995) which in turn blocks negative psychological states such as mental distress and depression (Teasdale et al., 2000). This process may modify the way traumatic memories are stored and transformed to an indelible state, possibly reducing the risk for chronic PTSD. Patients can achieve self-healing in this way.

The multilevel approach to treatment requires the inclusion of the patient in the recovery process. This involves addressing the meaning of the trauma and mental illness for the individual, as well as enrolling the patient in other aspects like medication compliance or changes in lifestyle. The disease model of PTSD carries the assumption that trauma is always bad; however, many individuals are resilient in the face of trauma, and others feel they are eventually able to grow through their experiences (Bonanno, 2004). Recovery models based on promoting the efficacy of the individual have potential promise (Bremner & Reed, 2014).

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CHAPTER 10

Childhood Exposure to Interpersonal Trauma

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Research in the past few decades has amply demonstrated the potential negative impact of traumatic experiences, particularly when abuse and maltreatment occur in childhood. However, definitions of these terms—trauma, maltreatment, and abuse—remain unclear and are still subject to debate. Who decides whether an event is traumatic? At what point does an experience become traumatic? What makes a particular parenting practice harmful? Does it need to result in marks and bruises to count as maltreatment? Some children might experience spankings as a normal part of the disciplinary practices in their household while for other children, physical punishments can create overwhelming fear and may be experienced as traumatic.

According to the *Diagnostic and Statistical Manual of Mental Health,* 5th ed. (*DSM-5*; American Psychiatric Association, 2013), the diagnosis of Posttraumatic Stress Disorder (PTSD) requires exposure to a traumatic event, defined as "exposure to actual or threatened death, serious injury, or sexual violence" (p. 271). This definition precludes childhood neglect and emotional abuse, which have been shown to lead to similarly negative consequences as physical or sexual abuse as well as other traumatic experiences (for a review, see Chu & Lieberman, 2010). The Child Abuse Prevention and Treatment Act (CAPTA) includes neglect in its definition of child abuse; neglect and emotional abuse are also recognized by most states as part of childhood maltreatment in addition to physical abuse and sexual abuse (U.S. Department of Health and Human Services, 2012). Thus, whether trauma includes neglect and emotional abuse remains inconsistent.

Though we recognize the importance of preventing childhood neglect and understanding its impact, due to the inconsistency in the literature we focus in this chapter primarily on acts of commission with particular emphasis on childhood abuse and witnessing domestic violence. We review the prevalence of childhood abuse and witnessing domestic violence, manifestations of these types of traumatic stress in childhood, and treatment programs for addressing posttraumatic responses. To fully understand the impact of trauma, we also need to understand many of the contextual factors that surround the potentially traumatic experience such as risk and protective factors in the child, the family, and the community. Thus, we examine these broad topics in relation to the many correlates that influence the experience of and reactions to trauma, such as social/cultural factors, attachment and caregiving contexts, and gene by environment interactions. Many research studies include both abuse and neglect as inclusion criteria for childhood maltreatment in their samples and do not distinguish between the two types of experiences (e.g., Cicchetti & Rogosch, 2012; DeBellis, Hooper, Woolley, & Shenk, 2010; Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Fang, Brown, Florence, & Mercy, 2012; Fisher, Ellis, & Chamberlain, 1999; Heim & Nemeroff, 2001). We employ the term *childhood maltreatment* when reporting

findings using samples that include both neglect and abuse. Neglect is discussed specifically where appropriate.

PREVALENCE: MEDIATORS AND MODERATORS

Childhood Abuse

In 2011, the national estimate of substantiated victims of childhood abuse and neglect reported to the state-level child protective service systems was 681,000 children, which translates to approximately 9.1 victims per 1,000 children aged birth to 18 in the population (U.S. Department of Health and Human Services, 2012). Though this number may appear to be relatively small in proportion to the total population, federal statistics are likely to include the more severe cases of childhood abuse and neglect. In 2011 the Center for Disease Control and Prevention (CDC) conducted a Youth Risk Behavior Survey and found that 11.8% of females and 4.5% of males reported forced sexual intercourse at least once in their lifetime (Eaton et al., 2012). The National Survey of Adolescents estimated that for youth between the ages of 12 to 17, 22% have experienced physical assault and 39% have witnessed domestic violence (Kilpatrick et al., 2003). Across numerous epidemiological and community-based studies, most estimates suggest that between 25 to 61% of children and youth have been exposed to at least one traumatic event (Copeland, Keeler, Angold, & Costello, 2007; Finkelhor, Turner, Ormrod, & Hamby, 2009). In these studies, traumatic events are widely defined and include (but are not limited to) child physical and sexual abuse, violence in families and communities, natural disasters and terrorism, accidental or violent death of a loved one, refugee and war experiences, impaired caregiving, and life-threatening injury and illness.

Age of Onset

Based on state-level child protective services data for the year 2011, children birth to 1 year of age had the highest rate of child maltreatment, with a rate of 21.2 per 1,000 children (U.S. Department of Health and Human Services; Administration for Children and Families, 2012). Of all child maltreatment victims, 27.1% were younger than 3 years of age while 20% were 3–5 years old. These rates of early childhood maltreatment seem to be on the increase. For example, 81.6% of all child fatalities in the year 2011 were younger than 4 years old, which was higher than the 75.7% of child fatalities younger than 4 years old in 2009 (U.S. Department of Health and Human Services; Administration for Children and Families, 2010). Consistent with these rates, infants are among the largest group of children to be placed in foster care. Infants also remain in foster care longer and experience more placements than children who are older (Wulczyn, Hislop, & Harden, 2002).

Some of the national population-based findings are in contrast to these official statistics which report that the rate of childhood abuse and neglect decreased with age (U.S. Department of Health and Human Services, 2012). Findings from one population-based sample of 4,549 children and youth aged 0–17 years recruited through random digit dialing for the National Survey of Children's Exposure to Violence suggest that physical abuse is relatively common across all age groups while sexual abuse and witnessing community assaults increase as age increases (Finkelhor, Ormrod, & Turner, 2009). Some researchers have suggested that the large population-based samples typically utilize retrospective parent reports versus substantiated cases of childhood maltreatment, which may introduce reporting bias into these prevalence rates.

Paying attention to childhood abuse rates as broken down by age group allows us to understand important trends beyond base prevalence rates. For example, in a three-wave longitudinal study with 1,467 children aged 2–17 recruited through random digit dialing to complete the Developmental Victimization Survey, findings suggest that polyvictimization (5+ types of victimizations) was most likely to occur within a 1-year period when children were 6 and 14 (Finkelhor, Ormrod, Turner, & Holt, 2009). These ages correspond roughly with school transitions (first grade and high school) when children are most likely to be distressed due to a new social and educational environment, thus more vulnerable to victimization.

Gender

Until the mid-1980s, few studies specifically examined male childhood sexual abuse. Since then, studies focusing on male sexual abuse have increased; however, research with sexually abused females continues to garner more attention than males. One contributing factor for this discrepancy may be that males are more reluctant than females to disclose abuse, due to struggles with the male ethics of self-reliance, stigma of homosexuality, and less likelihood to label certain childhood sexual activities with another individual as abusive (for review, see Romano & De Luca, 2001). Alternatively, females may be socialized to perceive (and report) violations in close relationships more so than males (DePrince & Freyd, 2002). In addition, mental health professionals continue to be biased against the existence of male sexual abuse; thus, professionals rarely ask adult males about childhood sexual abuse and

are reluctant to deal with child male victims (Romano & De Luca, 2001). Because systematic investigation of male childhood sexual abuse continues to be limited, comparisons between sexually abused males and females remain difficult to make.

Race/Ethnicity

Race and ethnicity disparities in the rates of childhood abuse persist. While some studies show a lack of group differences based on race or ethnicity (Elliott & Urquiza, 2006), child protective service records indicate consistent racial/ethnic differences in the referral rates for and number of substantiated cases of childhood abuse (U.S. Department of Health and Human Services; Administration for Children and Families, 2012). Researchers have pointed out that racial/ethnic group differences in prevalence rates may be influenced by a variety of factors, including acculturation levels, socioeconomic status, and neighborhood variables. One study showed that group differences between Black and White children in referral, substantiation, and entry to foster care rates were accounted for after adjusting for differences in socioeconomic and health factors (Putnam-Hornstein et al., 2013). Interestingly, Black children from low socioeconomic status families had a lower risk for referral, substantiation, and entry to foster care than their socioeconomically similar White peers. Similarly, among Latinos, children of U.S.-born mothers were significantly more likely than White children to come into contact with child protective services. However, once socioeconomic and health factors were included in the model, risk of referral, substantiation, and foster care entry was significantly lower for Latino children regardless of maternal nativity when compared with White peers.

Sexual Orientation

Another subgroup where prevalence estimates are hard to pinpoint is individuals who identify as gay, lesbian, or bisexual (GLB). Research findings have demonstrated that the prevalence rate of sexual victimization, and specifically childhood sexual abuse, are elevated in GLB individuals as compared with individuals who identify as heterosexuals (see Rothman, Exner, & Baughman, 2011). However, reported prevalence rates for GLB individuals range widely due to most studies utilizing convenience samples that are not generalizable. For example, a systematic review of studies with GLB individuals found the prevalence rate of childhood sexual abuse for males to range from 4.1% to 59.2% and for females to range from 14.9 to 76.0% (Rothman et al., 2011). The directionality between childhood abuse and sexual orientation also remains poorly understood despite the positive association found between childhood abuse and same-sex sexual orientation in adulthood due to the inability to create experimental designs to tease out causality.

Contextual Factors

Families living in poverty have more contact with system-based representatives and therefore may be more likely to have potentially abusive or neglectful behaviors reported to the authorities than wealthier families. In a healthy birth cohort of young children ages 1 to 3 years from an urban-suburban region, exposure to violence was particularly common among children living in poverty (Briggs-Gowan, Ford, Fraleigh, McCarthy, & Carter, 2010). The overall sample prevalence rate for violence exposure was 26.3% (14.5% noninterpersonal violence, 13.8% interpersonal violence) but when looking at the subsample of children living in poverty, the overall violence exposure rate increased to 49.0% (19.7% noninterpersonal violence, 33.7% interpersonal violence).

Many parental factors have been associated with increased likelihood of abuse such as young parental age, single parenthood, low education, low employment status, and psychopathology (see Oliver, Kuhns, & Pomeranz, 2006; Turner et al., 2012). Across these parenting factors that influence abuse risk, parental stress emerges as a common and potentially important variable (Chu et al., 2011).

Some additional common environment and social factors found to contribute to higher risk for childhood abuse include poverty-related factors (low income level, median residential housing/property value, unemployment, and low education), neighborhood structure (substandard or vacant housing, overcrowding, and residential instability; Coulton, Crampton, Irwin, Spilsbury, & Korbin, 2007). Neighborhood and environmental characteristics may influence social relationships within the community, which in turn may have an impact on childhood abuse risk. For example, residents in neighborhoods with greater social resources and community social network reported lower rates of childhood abuse (Coulton et al., 2007).

A substantial body of research continues to focus on identifying vulnerability and protective factors that moderate children's risk of abuse in the hopes of understanding the mechanisms underlying why and how childhood abuse occurs and how to prevent it from happening in the future (for a review, see Chu, Pineda, DePrince, & Freyd, 2011). However, as Stevens and Hassett (2007) point out, although we might understand the various factors that contribute to child abuse in identified patterns, abuse

often occurs in multiple contexts (families, neighborhoods, societies) which interact in complex and nonlinear ways that are not entirely predictable. Additionally, there are no identifiable factors that can absolutely protect a child from being abused.

Witnessing Domestic Violence

Estimates suggest that more than 3 million children witness some form of domestic violence (DV) each year (Straus, 1992). Reviews of the literature document a substantial co-occurrence of childhood abuse and witnessing DV, with 30–60% of families reporting both types of violence (Edleson, 1999; Margolin, 1998). Despite the large numbers of children exposed to DV, less than half of child welfare agencies indicate that they assess DV in reported childhood abuse cases (Hazen et al., 2007).

This lack of attention to DV exposure in the majority of child welfare protocols reflects a pervasive assumption that witnessing domestic violence does not constitute direct violence against the child. However, research evidence shows that exposure to DV negatively impacts children's development similar to abuse or neglect. For example, a recent review concluded that preschool children exposed to DV have difficulty expressing emotions, are more aggressive, and have less secure attachments than children without DV exposure (Howell, 2011).

Age of Onset

Pregnancy is a time of heightened risk for experiencing domestic violence for women. Pregnant women have approximately 35% higher risk of being a victim of domestic violence than nonpregnant women (Gelles, 1988). Domestic violence is also one of the most commonly reported trauma during pregnancy (Mendez-Figueroa, Dahlke, Vrees, & Rouse, 2013). Thus, if one considers the fact that DV also often occurs during pregnancy, the number of children impacted by DV is likely much greater than the prevalence rate currently suggests (Family Violence Prevention Fund, 2008). In turn, exposure to intimate partner violence during pregnancy is tied to negative medical conditions for both the mother and her infant, including later entry into prenatal care, low birth weight, premature labor, fetal trauma, and unhealthy maternal behaviors (for a review, see Jasinski, 2004).

Additionally, there may also be a delayed effect of DV exposure. In a sample of 3- to 5-year-old children who were part of the National Survey of Child and Adolescent Well-Being, those who had witnessed violence in the home during the ages of 3–5 (but not after age 5) showed no behavioral differences from those who had not witnessed DV during that same age period (Holmes, 2013). However, when followed prospectively, the group of children who were exposed to DV began showing increased aggression relative to the comparison group by the time they reached elementary school.

Gender and Sexual Orientation

Though research has established the pervasive impact of witnessing domestic violence, the majority of these studies have relied on samples of women from shelters for battered women (Edleson, 1999). While a large portion of DV victims are women, men can also be victims of DV (Strauss, 1992). Based on retroactive report, 50% of adults in a survey sample remembered their father hitting their mother during their teenage years while 19% recalled their mother hitting their father and 31% recalled both hitting the other. Additionally, the DV literature has been based on samples with heterosexual couples rather than same-sex couples. Therefore, we know little regarding the prevalence of or impact for children witnessing domestic violence where women are the perpetrators and men are the victims, or in families where the caregivers are in same-sex relationships.

Race/Ethnicity

National statistics suggest group differences based on race/ethnicity in experiencing domestic violence. For example, African American women appear to experience domestic violence at significantly higher rates when compared with Caucasian women, while Hispanic and Asian women report significantly lower raters of domestic violence as compared with Caucasian women (Rennison & Welchans, 2000). However, researchers and advocates have questioned whether the lower rates of DV in certain racial/ethnic groups are accurate estimates or perhaps the lower numbers might be due to under-reporting. Importantly, we also have little understanding regarding any differential impact of DV on children based on race/ethnicity variables.

Methodological Issues

Prevalence figures are often cited without great attention paid to the details in the operationalization of childhood abuse. Though researchers might uniformly agree that a 14-year-old child forced into sexual intercourse by an adult has been sexually abused, details within broad definitions are not always consistent. Some studies might include exposure, threats, and attempts while others may only focus

on more severe forms of abuse. As previously mentioned, samples with maltreated children have also often defined maltreatment history in a heterogeneous way, including neglect as well as emotional, physical, and/or sexual abuse. The age that separates childhood from adulthood abuse also differs widely across studies, with cutoffs ranging from 14 to 18 years (see Senn, Carey, & Vanable, 2008).

The majority of research to date dichotomizes the phenomenon of trauma, such that children are typically categorized into those who have or have not experienced childhood abuse. However, evidence is mounting to suggest that many children who are exposed to trauma actually experience multiple potentially traumatic events, including multiple types of abuse as well as other potentially traumatic events including (but not limited to) natural disasters, motor vehicle accidents, illnesses, war/terrorism, or death of a close other. A sample of urban children aged 3–6 admitted into community-based mental health or developmental services reported experiencing an average of 4.9 different *types* of potentially traumatic events (Crusto et al., 2010). Most operational definitions of trauma combine single versus multiple exposures, thus obscuring the true prevalence figures for single versus multiple exposures.

Studies that examine multiple victimizations utilize a broad define of victimization, including events such as child physical and sexual abuse, violence in families and communities, natural disasters and terrorism, accidental or violent death of a loved one, refugee and war experiences, impaired caregiving, and life-threatening injury and illness. While these methodological differences are to be expected, arriving at more convergence will serve to improve the rigor of our scientific pursuit.

SINGLE VERSUS CUMULATIVE TRAUMA

Multiple nationally representative samples reported similar rates of experiencing multiple types of victimizations. From the Developmental Victimization Survey, 7% reported seven or more types of victimizations by different perpetrators over the course of a single year, whereas 20% reported experiencing five or more types of victimizations (Finkelhor, Ormrod, & Turner, 2007). From the National Survey of Children's Exposure to Violence, 10.9% of children reported five or more direct exposures to violence in the past year (Finkelhor, Turner, Ormrod, & Hamby, 2009). A recent descriptive study on the core data collected by participating National Child Traumatic Stress Network (NCTSN) centers revealed a small but significant gender group difference in number of trauma types experienced, in that girls reported a higher mean number of trauma types as compared with boys (Briggs et al., 2013).

Epidemiological and clinical research has shown that the number of types of traumatic events exposed to in childhood is significantly correlated with the number and complexity of symptoms and diagnoses (see d'Andrea, Ford, Stolbach, Spinazzola, & van der Kolk, 2012). One of the seminal studies on cumulative risk comes from the study of Adverse Childhood Events (ACE's; Felitti et al., 1998). This prospective study showed that adults who at baseline reported four or more adverse childhood experiences were at greatly increased risk for negative physical and mental health outcomes over time. This pattern has been replicated numerous times, including a recent study where researchers found in an urban community clinic sample of 0–20-year-olds that increased number of ACEs was significantly correlated with increased risk of learning/behavior problems and obesity (Burke, Hellman, Scott, Weems, & Carrion, 2011). These findings are consistent with a growing body of literature indicating that developmental outcomes are best predicted by cumulative risk factors rather than by a single pathogenic condition (Rutter & Sroufe 2000).

In addition to cumulative risk factors, some researchers are also starting to examine the cumulative effect of trauma over time and across systems of functioning, otherwise known as the developmental cascades theory. The developmental cascades theory refers to the "cumulative consequences for development of the many interactions and transactions occurring in developing systems that result in spreading effects across levels, among domains at the same level, and across different systems or generations" (Masten & Cicchetti, 2010, p. 491). This approach suggests that antecedent conditions may yield varying probabilities for developing specific subsequent outcomes (Cox, Mills-Koonce, Propper, & Gariepy, 2010). The varying trajectories depend on the timing for development within and across various systems as well as the context within which the development is disrupted. In other words, functions at a basic level can impact functioning at higher levels through a spreading (or snowballing) effect or impact functioning over time on a domain that develops later in the developmental stage. The developmental cascade model proposes that developmental psychopathology results from the compounding of risk and protective factors. Earlier competencies or disruptions in functioning confer additional risk for the later development of adaptive or maladaptive behaviors.

MANIFESTATIONS AND CHILD OUTCOMES

Biological Manifestations

Brain Anatomy and Physiology

The two brain structures most often researched in children are the hippocampus and the amygdala (for a review, see Teicher et al., 2003). The hippocampus is implicated in the encoding and retrieval of information, most commonly studied in conjunction to learning and memory functioning. The amygdala is involved in evaluating potentially threatening information, fear conditioning, emotional processing, and memory for emotional events. The amygdala is also involved in the output of stress hormones which also impacts the hippocampus. Another brain region receiving increasing attention is the prefrontal cortex (PFC) for its role in many aspects of behavior, cognition, and emotion regulation.

Hippocampus. One meta-analysis indicated that hippocampus volumes were not significantly different when comparing maltreated children with PTSD to a control group of children without PTSD (Woon & Hedges, 2008). However, the same meta-analysis found that reduced bilateral hippocampus volume was found in adults with childhood maltreatment-related PTSD compared with healthy individuals. Interestingly, more recent longitudinal studies have found differences in the hippocampus of traumatized youths. Severity of PTSD and high cortisol levels predicted reductions in hippocampus volume over a 12- to 18-month interval (Carrion, Weems, & Reiss, 2007). Inconsistencies between the adult and child literature may be due to developmental processes or a latent effect where structural differences emerge over time during adolescence into adulthood. Supporting this idea, rat studies show that differences in hippocampus emerged only after young adulthood (Andersen & Teicher, 2004).

Amygdala. Neuroimaging studies also suggest that there are no amygdala volume differences between traumatized youth with PTSD and healthy controls (see Carrion & Kletter, 2012). One study found a 5.1% reduction in amygdala volume of maltreated youth compared with healthy controls, but when results were corrected for total brain gray matter, no significant differences remained (Carrion et al., 2001). Woon and Hedge's (2008) meta-analysis supports the general consensus that amygdala volumes are not significantly different when comparing maltreated children to healthy controls.

Prefrontal Cortex. Findings comparing the prefrontal cortex (PFC) volume of children with maltreatment and healthy controls are also mixed. One study reported no group difference (DeBellis et al., 1999), but another found smaller prefrontal volume and prefrontal white matter (DeBellis et al., 2002) in the maltreated group. Maltreated youth did not show the typical frontal lobe asymmetry (Carrion et al., 2009) due to the maltreated youth having larger left frontal lobe volume than healthy controls. Two other studies found larger gray matter volume of the middle-inferior and ventral regions of the PFC in children with PTSD (Richert et al., 2006; Carrion et al., 2009). One study examined the relationship between cortisol and the PFC in children exposed to interpersonal trauma versus children who were not exposed to interpersonal trauma (Carrion, Weems, Richert, Hoffman, & Reiss, 2010). Results showed that children exposed to interpersonal trauma and reporting PTSD symptoms had decreased ventral and left inferior prefrontal gray volumes. Furthermore, this decrease in PFC volume was associated with elevated bedtime cortisol levels.

In summary, knowledge is still in its early stages in this area. The brain continues to develop in the first 25 years of life; peak volumes of various brain structures occur in late childhood or early adolescence (see Giedd 2009). Consistent with the developmental cascade theory, concurrent psychopathology or adverse events during early childhood years can contribute to more heterogeneous physiological outcomes. Thus, the nature and timing of the adverse events during normal development can lead to different patterns of physiological response (Andersen et al., 2008).

Caregiving Context. The impact of the caregiving environment on brain structures remains an open question. There is almost no research available about the effects of witnessing domestic violence on brain development. There is also limited research on whether an enriched caregiving environment may play important roles in reversing the deleterious effect of trauma on brain structures. One longitudinal study showed that maternal support during a mildly stressful interactive task in early childhood (ages 3–5) predicted larger bilateral hippocampus volume at ages 7–13 (Luby et al., 2012). A randomized clinical trial with premature infants also demonstrated that early environmental enhancement in the neonatal intensive care unit was associated with positive changes in brain structure and functioning (Als et al., 2004).

Methodological Issues. Studies on children who experienced institutionalized care (e.g., Bucharest Early Intervention Project) provide a wealth of information on the impact of neglect and adversity on brain structures and functioning. However, we do not report on this

vast literature because the co-occurrence of childhood abuse with the neglect experienced during institutionalized care has not been clearly documented. This is a prime example regarding the lack of knowledge on the specific experiences of children in terms of the co-occurrence of neglect with instances of abuse that might be unreported or unidentified.

One additional complication in interpreting results on brain structures is that many studies conflate the experience of trauma with a diagnosis of PTSD. Many studies of adults and children have tended to recruit individuals with PTSD and compare to a group of participants without PTSD. This approach makes it difficult to tease apart effects unique to maltreatment experience (e.g., individuals with trauma histories but without PTSD) and current psychopathology.

Traditionally, the focus has been on how traumatic stress might impact cell development and brain structures, otherwise known as the neurotoxicity hypothesis. Specifically, the neurotoxicity hypothesis suggests that stress-induced prolonged exposure to glucocorticoids may lead to a reduction in cell complexity or cell death (Sapolsky, Uno, Rebert, & Finch, 1990). More recently, researchers are taking a further step to examine how structural differences might in turn present as a risk factor for persistent PTSD symptoms going into adulthood, otherwise also known as the vulnerability hypothesis (Teicher et al., 2003). In a twin study, Gilbertson et al. (2002) found that combat veterans with persistent PTSD symptoms had smaller hippocampus volumes than combat veterans without PTSD. However, the nontrauma exposed identical twins of the combat veterans with PTSD also had reduced hippocampus volumes, suggesting that the reduced hippocampus volumes may have preceded the development of PTSD symptoms. Additional twin studies and/or longitudinal designs are needed to further elucidate the directionality and time course of these processes.

The distinction between brain structural changes and functional anomalies also need to be better understood. DeBellis et al (2010) found in a sample of children aged 3–18 years that PTSD symptoms was significantly associated with poorer visual memory (typically associated with hippocampus functioning) although hippocampus volumes did not predict PTSD symptoms. Youth exposed to interpersonal trauma and reporting PTSD symptoms had increased amygdala activation in response to threatening facial expressions when compared with healthy controls (Garrett et al., 2012). Other recent fMRI studies demonstrated that children with experiences of maltreatment or family violence showed greater activation in the amygdala when viewing angry faces as compared with neutral faces (McCrory et al., 2011) or as compared with children without maltreatment histories (McCrory et al., 2013). These findings suggest that functional anomalies may occur prior to any evidence of structural differences.

HPA System/Cortisol

Most research studies on how violence and trauma can impact the human brain focus on stress responses in the HPA axis and the effects of cortisol, a potent stress hormone in the body (for a review, see Bevans et al., 2005). The catecholamine system/sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis are the body's major stress systems (see Bevans, Cerbone, & Overstreet, 2005; DeBellis et al., 1999; Schore, 2002). The catecholamine system is located in the brainstem and begins to develop very early in life. The release of corticotropin-releasing hormone (CRH) by the hypothalamus stimulates the catecholamine system. This in turn causes the locus coeruleus to release norepinephrine and the adrenal gland to release adrenaline and noradrenaline. These hormones affect the body's stress response by increasing blood pressure, heart rate, and perspiration. The HPA axis also works with the catecholamine system and mediates the fight–flight response. Like the catecholamine system, the stress response in the HPA axis begins when the hypothalamus produces and secretes CRH. CRH then stimulates the anterior pituitary gland to release adrenocorticotrophic hormone (ACTH) which in turn stimulates the production of glucocorticoids such as cortisol. In examining these systems, researchers typically examine the diurnal pattern of cortisol basal levels or cortisol reactivity to acute stressors.

In daily functioning, cortisol helps to maintain the timing of activities such as waking, sleeping, eating, and social interactions (Gunnar & Quevedo, 2007). The HPA axis follows a circadian rhythm; in typical development cortisol level is high in the early morning (with a peak within 30 minutes of waking up), sharply decreases by midmorning, and further declines throughout the day to the lowest level at bedtime. A circadian pattern of cortisol production typically emerges in the first few months of life. However, cortisol levels do not become stable or consistently predictable until children are about 4 years old (Bruce, Davis, & Gunnar, 2002; Gunnar & Quevedo, 2007; Watamura, Donzella, Alwin, & Gunnar, 2003). The pattern then maintains throughout the rest of the life span. As a result, we know little about the impact of trauma on cortisol levels in this developmental age range.

Another aspect of cortisol that is important to consider is the response after acute stress. An increase in cortisol in response to stress is adaptive and important for survival because it activates the fight or flight response. During a stress response, increases in cortisol levels produce additional energy and focus attention toward the stressor while postponing processes that are less important for immediate survival like immune response, growth, reproduction, digestion, and tissue repair (Johnson, Karmilaris, Chrousos, & Gold, 1992). From birth until about 4 months of age, infants reliably demonstrate a rise in cortisol in response to lab-based stressors, but by 6 months of age, similar stressors elicit increases in cortisol less reliably, and by 12 months, it is even more difficult to reliably elicit an increase in cortisol (for reviews, see Gunnar, Talge, & Hererra, 2009; Jansen, Beijers, Riksen-Walraven, & de Weerth, 2010).

Though a certain amount of activation in response to stress is adaptive, chronic exposure to stress can alter the overall development and functioning of the HPA system (Bremner & Vermetten, 2001; Gunnar & Vazquez, 2001). In turn, HPA system dysregulation is associated with significant health problems, cognitive functioning, and psychosocial disorders (DeBellis et al., 1999; Heim & Nemeroff, 2001). However, a review of cortisol data indicates that results across the age range are mixed on whether maltreatment leads to a hyperactivity in the HPA axis or hypoactivity (see McCrory, De Brito, & Viding, 2011). In recent years, researchers are beginning to suggest that a better representation of HPA axis functioning after experiencing trauma may be that both hyper- and hypoactivity are involved (McCrory et al., 2011). Studies are now turning to factors that might impact the dysregulation for both hyperfunctioning and hypofunctioning to understand why different response patterns emerge.

One study found that infants and toddlers less than 24 months of age in foster care (after having experienced abuse or neglect) showed higher baseline cortisol production compared with children not in foster care (Dozier, et al., 2008). However, in an older preschool aged sample, a small number of preschoolers had high levels of cortisol while most preschoolers in foster care exhibited lower levels of cortisol as compared with healthy children of the same age (Fisher et al., 2000). Researchers have suggested that the HPA axis may down-regulate in response to prolonged hyperactivation (e.g., Fries, Hesse, Hellhammer, & Hellhammer, 2005; Gunnar & Fisher, 2006). A meta-analysis with 107 studies of primarily adult samples indicated that chronic stress initially produced elevated cortisol, which rebounds to below normal levels as time passes after the stressor is removed (Miller, Chen, & Zhou, 2007). Though longitudinal studies have yet to be conducted to examine this hypothesis with children, adult findings suggest a change in HPA axis functioning based on the temporal timing of the stressor (i.e., time since onset or removal of stressor).

Researchers have also argued that early trauma experiences may lead to both hypo- and hyperreactivity in the HPA system because early chronic stressors may blunt overall basal HPA axis activity, but the system may be hyperreactive to acute stressors (e.g., DeBellis, 2001; Loman & Gunnar, 2010). For example, preschool children show an increase in cortisol reactivity across the first week of starting school, seen as a healthy adaptation to a naturally-occurring stressor (Graham et al., 2012). However, children in foster care show an even greater increase in cortisol reactivity in response to the start of preschool as compared with children not in foster care (Graham et al., 2012). The authors surmised that these findings suggest that dysregulation of the HPA axis for children with maltreatment histories might be characterized by an extended or a delayed cortisol response to stressors.

Additional work by Cicchetti and colleagues suggest that HPA axis dysregulation may depend on the presence of co-occurring internalizing or externalizing symptoms. In a sample of 553 children aged 7–13, those with early onset physical or sexual abuse and with high depressive or internalizing symptoms exhibited an attenuated diurnal decrease with lower morning basal level and higher afternoon basal level as compared with other children with later onset physical or sexual abuse or early occurring neglect or emotional abuse (Cicchetti et al., 2010). Due to the fact that most studies are cross sectional, the time sequence of comorbid conditions remains unknown. In other words, it is not clear whether psychopathology leads to HPA axis dysregulation, or if hyper/hypoactivity in the HPA axis leads to psychosocial difficulties. One longitudinal study that began to address this question examined social functioning and cortisol regulation in a sample of school-age maltreated and nonmaltreated children who attended a week-long summer camp for 2 consecutive years (Alink, Cicchetti, Kim, & Rogosch, 2012). Results indicated that lower levels of prosocial behavior and higher levels of disruptive/aggressive behavior were significantly associated with lower morning cortisol levels 1 year later. Withdrawn behavior was significantly related to higher afternoon cortisol levels 1 year later. Additional longitudinal studies are needed to determine if the altered HPA axis functioning may indeed lead to additional difficulties later in life.

Little is known about how additional characteristics of the traumatic event itself (such as recency of traumatic event or trauma type) or of the individual (e.g., gender) might impact the HPA response. Recency of the traumatic event may be one of the factors that impact HPA functioning. Pervanidou and colleagues (2007) found that after a motor vehicle accident, children (with PTSD) initially had elevated evening salivary cortisol, which then normalized in the 6 months after the trauma. In a sample of youth exposed to interpersonal violence, a higher level of salivary cortisol was also positively associated with PTSD among individuals with recent traumas in the previous year. However, for youth who reported distal traumas of more than a year prior to assessment, the more PTSD symptoms the lower the level of cortisol (Weems & Carrion, 2007). Another study showed down-regulation of cortisol production in girls with more pervasive maltreatment and girls who experienced maltreatment that was early onset and not recent (Doom, Cicchetti, Rogosch, & Dackis, 2013).

Cortisol patterns also may vary by trauma type, or the nature of the stressor. Physical and sexual abuse have been associated with high morning cortisol levels in children while those who have suffered multiple types of abuse are more likely to exhibit high morning and afternoon cortisol levels (Cicchetti & Rogosch, 2001). Miller and colleague's (2007) meta-analysis with adult samples suggested that stress that threaten physical integrity (e.g., combat) may impact the HPA system differently than threat to the social self (e.g., divorce). This hypothesis has not yet been tested in young children, but a parallel example might be threats to the caregiver.

Research is just beginning to examine gender differences in cortisol and HPA axis functioning. Elevated daily cortisol levels were reported for boys compared with girls in the group with more pervasive maltreatment. Boys with less pervasive maltreatment had lower DHEA and higher cortisol/DHEA ratio levels than girls with similar experiences, nonmaltreated boys, and boys with more pervasive maltreatment (Doom et al., 2013). Additional studies are sorely needed to better understand how additional contextual variables might impact the stress response of the HPA axis.

Caregiver Context. Not surprisingly, the caregiving environment plays an important role in the development of the HPA system and stress response for children. Recent advances in methodology has greatly contributed to our understanding of how maternal distress impacts the intergenerational transmission of traumatic stress via in vitro fetal exposure to increased cortisol (see Field, Diego, & Hernandez-Reif, 2006, for a review). When exposed to elevated maternal prenatal cortisol as a result of not only traumatic stress but also moderate levels of stress, the offspring experiences prenatal, perinatal, and postnatal complications including lower fetal weight delayed growth. In turn, these alterations can lead to a host of psychosocial difficulties and health conditions.

Furthermore, infants at 6 months of age whose mothers had a history of childhood abuse have been found to have significantly lower levels of baseline cortisol (Brand et al., 2010). In a sample of mother–infant dyads, maternal PTSD following the September 11 attacks was associated with significantly lower infant baseline cortisol levels at 9 months of age (Yehuda et al., 2005). Maternal depression has also been found to be significantly associated with increased levels of baseline cortisol levels in infants (Brennan et al., 2008). Morning salivary cortisol in adolescents who had been exposed to maternal postnatal depression was found to be elevated and more variable compared with nonexposed peers, a pattern associated with an increased risk of depression (Halligan, Herbert, Goodyer, & Murray, 2004).

Fisher and Stoolmiller (2008) also reported that one predictor of foster care preschool children's lower early morning cortisol levels was the stress level reported by foster caregiver. If a foster caregiver reported being highly stressed by the child's behavior on a given day, the child had lower cortisol levels the following morning relative to his/her levels on other days. Bernard, Butzin-Dozier, Rittenhouse, and Dozier (2010) compared cortisol production patterns in children remaining with birth parents to children placed in foster care following involvement of child protective services. Results showed lower waking cortisol levels and flatter diurnal slopes in both groups (compared with a control group of low risk children), with the flattest slopes in the group of children who continued to live in the high stress environments with their birth parents.

In terms of acute stress response, history of early maternal sexual and physical abuse and comorbid PTSD was associated with greater increases in infant cortisol levels in response to a laboratory stress task (Brand et al., 2010). Co-occurring maternal depression and anxiety was also significantly associated with increases in infant cortisol reactivity (Brennan et al., 2008). Disorganized infants showed cortisol increase in response to the Strange Situation tasks as compared with a play task (Bernard & Dozier, 2010). Organized infants did not show cortisol reactivity to either task.

Biological Context. Specific candidate genes that may play a role in explaining variability in cortisol reactivity have been identified. Infants with one or two T-alleles of the FKBP5 SNP and an insecure-resistant attachment showed a two-fold risk for heightened cortisol reactivity during the Strange Situation Procedure (Luijk et al., 2010). In a study with 6-month-old twins, when in the context of high family adversity cortisol levels was accounted for by genetic factors, and to a lesser extent by unique environmental factors. In low family adversity context, however, there was no genetic contribution and only environmental contributions to the cortisol levels (Ouellet-Morin et al., 2009). In a sample of maltreated and nonmaltreated children aged 6 to 12 years, those with two copies of the CRHR1 TAT haplotype showed an attenuated slope in cortisol across the day compared with maltreated children with zero or one copy of the TAT haplotype (Cicchetti et al., 2011). These same children with two copies of the CRHR1 TAT haplotype were also not different from nonmaltreated comparison children. The 5-HTTLPR gene did not impact cortisol dysregulation.

Genetics

Genetic polymorphism refers to the existence of more than one allele, or form of a portion of a gene. Polymorphisms in the dopaminergic, serotonergic, and oxytonergic systems have received increased attention in recent years. In the following sections, we review some of the more commonly studied gene by environment interactions in relation to childhood abuse.

Serotonin Transporter. The serotonin system is involved in affect and emotion regulation, with the serotonin transporter (5-HTT) gene facilitating the utilization of serotonin (5-HT). The polymorphism of this gene in the promoter region (5-HTTLPR) involves the short (s) or long (l) alleles in three possible configurations: s/s, l/l, and l/s. The short allele (s) has been linked to reduced 5-HTT transcription, lower 5-HTT protein levels, and diminished serotonin re-uptake compared with individuals with the long (l) allele. Thus, in response to stressful life events or trauma in childhood, the l/l genotype has been found to confer the highest level of resilience while the ss form has been found to be associated with the greatest vulnerability to depression and other psychiatric disorders (e.g., Caspi et al., 2003; Kaufman et al., 2006).

Dopamine Receptor. The dopaminergic system is involved in attention, motivation, and reward mechanisms (Robbins & Everitt, 1999). The dopamine receptor D4 is encoded by the DRD4 gene, which has a number of polymorphisms. One is a 48-base pair tandem repeat (48 bp VNTR in the coding region of the gene (exon 3). The 48 bp VNTR alleles range from 2 to 11 repeats. Receptor molecules coded by the 7-repeat allele have been shown to react less strongly to dopamine molecules as compare to the other frequent repeat alleles.

Studies have found an association between the 7-repeate allele and various outcomes in children including ADHD, aggressiveness, and temperament (e.g., Cicchetti, Rogosch, & Toth, 2011; LaHoste et al., 1996). Findings have also suggested an association between the 7-repeat allele and disorganized attachment behavior (e.g., Lakatos et al., 2000). In the longitudinal Budapest Infant-Parent Study, the 7-repeat variant of the 48 bp VNTR polymorphism was overrepresented in 1-year-old infants displaying disorganized attachment behavior with their mothers in the Strange Situation Procedure (Spangler, Johann, Ronai, & Zimmermann, 2009). The 7-repeat allele was found in 67% of infants with disorganized attachment versus 20% in infants with secure attachment and 50% in infants with avoidant and resistant attachments. The estimated risk among children carrying the 7-repeat allele for disorganized attachment was fourfold.

However, some questions regarding this association remain. A Dutch twin study failed to replicate this finding (Bakermans-Kranenburg & Van IJzendoorn, 2004). Some findings also suggest that this association is only when infants are reared by mothers who suffer from unresolved trauma and loss, in which case there is an almost 19-fold increased risk for disorganized attachment (Van IJzendoorn & Bakermans-Kranenburg, 2006). Additional data suggest that this association was significant only when the single nucleotide polymorphism (SNP) -521 C/T, another common polymorphism, was present in the promoter region of the DRD4 gene (Lakatos et al., 2002; Gervai et al., 2005).

Catecol-O-methyltransferase. Another common functional polymorphism is in the coding region of the catecol-O-methyltransferase (COMT) protein enzyme, which metabolizes catecholamines (e.g, dopamine, epinephrine, norepinephrine). This polymorphism involves a substitution of valine (Val) by methionine (Met) at codon 158 (Val-158-Met). The Met allele is associated with a fourfold reduction in enzyme activity compared with the Val allele (Scanlon, Raymond, & Weinshilboum, 1979). A protective effect has been reported for COMT heterozygotes (Val/Met) showing dopamine levels associated with optimal neurobehavioral outcomes, compared with both

homozygous groups (Wahlstrom, White, & Luciana, 2010). These differing levels of dopamine activity influences functions regulated by catecholamines, including reactivity in the HPA axis (Oswald, McCaul, Choi, Yang, & Wand, 2004). A study examining two large population samples found that disorganized attachment scores were higher in carriers of the Val/Met genotype as compared with the Val/Val and Met/Met carriers (combined effect of $d = 0.22$; Luijk et al., 2011).

Brain Derived Neurotropic Factor. The brain-derived neurotrophic factor (BDNF) factor supports the survival and growth of neurons in the central nervous system and the peripheral nervous system. In a sample of 8- to 13-year-old children who had lived in institutional care prior to being adopted by 6 years of age, the BDNF gene moderated attention problems and duration of institutional care (Gunnar et al., 2012). Results showed that ADHD scores were lower for children adopted within the first year of life and that ADHD scores increased as adoption age increased. Specifically, children with at least one Met allele of the Val66Met genotype had lower ADHD symptoms when adopted at a younger age and higher ADHD symptoms when adopted at an older age, resulting in a more marked association between age at adoption and ADHD symptoms. This finding suggests that children with at least one Met allele supports the development of attention regulatory competence at short durations of adversity but suppresses the development of attention regulatory competence at long durations of adversity.

Corticotropin Releasing Hormone Receptor. The corticotropin releasing hormone receptor 1 (CRHR1) gene is the key activator of the HPA axis. Polymorphisms of the CRHR1 are major determinants as to whether early-life trauma is associated with depression (Bradley et al., 2008). The impact of this gene also appears to occur in a sex specific manner. One study with a birth cohort from England showed that males with childhood trauma and a protective polymorphism had reduced cortisol response; however this buffer effect was not present in females (Heim et al., 2009).

Multiple Gene Interactions. Beyond the impact of single genes, some studies have also started looking at potential interactions of multiple candidate genes. In two large population samples (Generation R Study and the NICHD Study of Early Child Care and Youth Development), no consistent evidence emerged for additive effects of candidate genes involved in attachment security and disorganization (Luijk et al., 2011). However, other studies have found interaction effects of multiple genes for other types of outcomes.

Cicchetti and Rogosch (2012) examined in a sample of maltreated and nonmaltreated children aged 6 to 12 years from low income families four candidate genes: 5-HTT, DRD4–521 C/T SNP, OXTR, and CRHR1 (corticotropin releasing hormone receptor 1). Results indicated that genetic variation has a negligible effect for maltreated children in predicting resilient functioning. However, having specific genotypes (5-HTTLPR: s/s genotype variant, CRHR1: zero copies of the TAT haplotype for, DRD4–521 C/t SNP: TT genotype variant, and OXTR: AA or AG genotypes) contributed to higher resilient functioning in nonmaltreated children as compared with maltreated children with the same genotype. In this same sample, maltreated children who had two copies of the TAT haplotype of the CRHR1 and the l/l genotype of the 5-HTTLPR had higher levels of depression symptoms than nonmaltreated children with the same combination (Cicchetti, Rogosch, & Oshri, 2011). For children with two copies of the TAT haplotype of CRHR1 and the s/s or s/l genotype of the 5-HTTLPR or for children with zero or one copies of the TAT haplotype of CRHR1, maltreatment status was not associated with level of depression symptoms.

In a different sample, children with or without maltreatment history were examined for an interaction between the BDNF gene and the 5-HTT gene (Kaufman et al., 2006). Results indicated that genetic vulnerability associated with these two genetic variations was present only in maltreated children. Specifically, maltreated children with the Val66Met polymorphism of the BDNF gene and the *s*/*s* genotype of the 5HTTLPR had the highest depression scores as compared with maltreated children without this genotype or nonmaltreated children. The s/s 5HTTLPR genotype was associated with an increase in maltreated children's depression scores, which was greatest for the children without positive supports and the additional presence of the Val66Met allele of the BDNF polymorphism. A recent study also found a similar interaction between CRH-R1 and 5HTTLPR polymorphisms in moderating depression risk after childhood trauma (Ressler et al., 2010).

Gene by Environment Interactions. There has been a burgeoning of studies examining the interplay between trauma, genes, and the environment in terms of how early experiences might influence the expression of genetic coding. Caspi et al.'s (2002) landmark study on children with histories of childhood maltreatment and genotypes of the

enzyme monoamine oxidase A (MAOA) was one of the first to examine this gene by environment interaction. This study found that children with maltreatment histories who are carriers of the low activity MAOA allele were more likely to develop antisocial behavior as they grew older as compared with maltreated children who are carriers of the high activity MAOA allele. Subsequent research has provided additional support that there are no specific genes for inheriting disorders such as PTSD, depression, or antisocial behavior. Instead, genetic variants each add a small increment to the probability that someone may be vulnerable to or be protected from developing a psychiatric condition.

Several models have been proposed for gene–environment interactions. One of the more commonly described models is the diathesis–stress model, which proposes that genes that increase vulnerability (or resilience) are more likely to be expressed within adverse or stressful environments versus more favorable conditions. Recently, a differential susceptibility model has also gained traction (Belsky, 1997, 2005). The differential susceptibility model posits that children with certain biological or genetic predispositions are more susceptible to variations in the environment and respond more strongly than other children to both negative and positive environmental influences. Yet a third area focuses on how environmental influences can serve to regulate genetic expression by mediating both maladaptations as well as adaptations; otherwise known as epigenetics (Tsankova, Renthal, Kuman, & Nestler, 2007).

According to the diathesis stress model, children with a genetic vulnerability are disproportionately likely to be affected adversely by environmental stressors. In the absence of environmental adversity, the genetic vulnerability is not expressed, in which case these children are similar to those without the genetic risk. Extensive research supports this model.

The likelihood of having a disorganized attachment was significantly greater in infants who had the short allele polymorphism of the 5-HTT transporter gene and whose mothers exhibited low responsiveness (Spangler et al., 2009). In a study of more than 2,000 pairs of female twins, the presence of a traumatic stressor increased the probability of developing major depression in twins who were at low genetic risk for depression from 0.5 to 6.2% (Kendler et al., 1995). In twins who were at high genetic risk the likelihood of developing depression increased from 1.1 to 14.6%.

Though the diathesis-stress model focuses on the negative impact that adverse environments can have on genetic vulnerability, positive environments can also buffer genetic risk. Kaufman et al. (2006) demonstrated that children with environmental risk (maltreatment) and genetic vulnerability (the s/s genotype and BDNF met allele) for developing depression were buffered if they had social support. Another study examined infants with a short allele genotype (s/s or s/l), a genetic risk for insecure attachment, and their mothers during the Strange Situation Procedure at 15 months of age (Barry, Kochanska, & Philibert, 2008). Results showed that mothers who showed low responsiveness during the Strange Situation Procedure predicted particularly high risk for insecure attachment in the infants while mothers who showed high responsiveness offset the risk for insecure attachment. For infants with the l/l genotype variant, mother's level of responsiveness was not associated with infant attachment. Similarly, among children with the short allele genotype variant (s/s or s/l), those with insecure attachment developed poor regulatory capacities while those who with secure attachment developed as good regulatory capacities as children with the l/l genotype variant. This finding demonstrates that a secure attachment relationship can serve as a protective factor in the context of genetic vulnerability.

Unlike most gene by environment interactions that focus primarily on negative outcomes, the differential susceptibility model suggests that variations in experience may lead to worse or *better* outcomes based on genetic predispositions. In other words, children with high genetic risk in the context of negative environments show particularly negative outcomes while these same children in positive environments show better outcomes as compared with children without the genetic risk. This model has particular implications on treatment responsiveness, as discussed in a later section.

Epigenetic mechanisms refer to processes by which environmental influences, such as caregiving, can regulate gene activity (e.g., gene expression) without altering the DNA sequence. One often studied mechanism is DNA methylation, which alters the expression of genes in cells during cell division. DNA methylation occurs by either creating a barrier to transcription factor binding proteins or by recruiting proteins that generate a different shape for the methylated region of DNA. Whole-genome DNA methylation was studied in a sample of 7- to 10-year-old children, either raised in institutional care or with biological parents (Naumova et al., 2012). Results showed greater methylation in the institutionalized group relative to the biologically raised group. Methylation differences were found in genes involved in the control of immune response and cellular signaling systems, including neural

communication as well as brain development and functioning. One longitudinal study involved 15-year-old adolescents with parent reports of stress adversity during their child's infancy and preschool (Essex et al., 2013). Findings showed that greater levels of maternal stressors in infancy and paternal stressors in preschool years predicted higher levels of methylation at DNA methylation sites. This not only supports the occurrence of epigenetics but also suggests that epigenetic modifications have period-specific sensitivity sequentially dependent on maternal versus paternal stress. These data also support findings from a previous study where DNA methylation in 5-year-old children was also associated with maternal smoking during the intrauterine period (Breton et al., 2009).

Findings from these human studies also replicate results from animal research. A recent study employed a rodent model in which infant rats were exposed to caretakers under stress that showed abusive behaviors (Roth, Lubin, Funk, & Sweatt, 2009). Early maltreatment produced persisting changes in methylation of BDNF DNA which in turn altered BDNF gene expression in the PFC and hippocampus later on in adulthood. This finding is of particular interest as it documents the epigenetic effects of maltreatment in brain areas that are known to be both structurally and functionally altered in adults following maltreatment. Roth et al. (2009) also observed altered BDNF DNA methylation in the offspring of these females that had previously been exposed to maltreatment as pups. This suggests the possibility of a transgenerational transmission of epigenetic changes in gene expression even when the next generation had not been exposed to such environmental stressors.

Cellular Aging

Another area of biogenetic research that has received increasing attention in recent years as a potential mechanism between early life adversity and subsequent deleterious outcomes is cellular aging, or the changes in cells that occur over the life span. In particular, the length of telomeres, which are DNA repeats that cap the ends of chromosomes and promote stability, has become an important biomarker of cellular aging (Blackburn, 2001). As cells divide, telomeres get shorter, leaving the cell vulnerable to genomic instability, end-to-end chromosome fusion, and mitosis and cell replenishment dysfunction (Blackburn, 2001).

A burgeoning area of research has focused on risk factors for and correlates of shorter telomere length. For example, greater cortisol responses to an acute stressor and flatter day-time cortisol slopes were associated with shorter telomere lengths (Tomiyama et al., 2011). In turn, the shortening of the telomeres has been shown to be a risk factor for chronic age-related diseases and early mortality (Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003) as well as a host of psychiatric conditions (for review, see Price, Kao, Burgers, Carpenter, & Tyrka., 2013).

Importantly, a number of retrospective studies have shown that a history of childhood abuse and neglect is significantly associated with shorter telomeres. Tyrka and colleagues (2010) were the first to demonstrate this link in adults with or without a history of childhood maltreatment. Since that time, several other studies have replicated this finding (for a review, see Price et al., 2013). A recent longitudinal prospective study also demonstrated that children exposed to two or more traumatic stressors (such as domestic violence, bullying, abuse or neglect) at age 5 had significantly shorter telomeres at age 10 compared with same-aged peers exposed to less or no violent stressors after adjusting for sex, socioeconomic status, and body mass index (Shalev et al., 2013).

More recent research suggests that not only is there a link between shorter telomere length and childhood abuse and neglect but this association appears to be impacted by cumulative traumatic stress. In a sample of young to middle-aged adults, those with PTSD had shorter telomeres than same-aged peers without PTSD (O'Donovan et al., (2011). However, this association was driven by individuals with PTSD who had been exposed to multiple types of childhood trauma. In other words, individuals with PTSD who had none or one category of childhood trauma did not have significantly different telomere lengths than control participants without PTSD. Furthermore, greater number of categories of trauma exposure prior to age 14 was significantly related to shorter telomere lengths. Though telomere length is becoming an important biological marker of aging and the impact of traumatic stress, the ability to prevent or reverse telomere shortening remains an open question.

Psychosocial Manifestations

Attachment

Young children evolve their feelings of safety in the world around the physical and emotional availability of the attachment figure, monitoring the environment for signs of danger and seeking proximity and contact when faced with threat (Bowlby, 1969). In the moment of trauma, the child experiences overwhelming sensory stimulation in the form of pain and/or frightening visual, auditory, olfactory, and tactile sensations. An attachment figure who

is available to the child under conditions of risk and stress can buffer the child's response, whereas an unavailable or frightening attachment figure can exacerbate the child's fears. Several studies have shown that infants in secure attachment relationships are better able to modulate their physiological stress response as compared with infants in insecure attachment relationships, whereas infants with anxious or disorganized attachment are associated with greater dysregulation of physiological response (Gunnar & Cheatham 2003; Gunnar & Quevedo 2007). This pattern appears to extend into adulthood. A study with young adults showed that adult attachment in current close relationships mediated the relationship between childhood abuse and current symptoms (Muller, Thornback, & Bedi, 2012).

In addition to symptoms, attachment also appears to impact cognitive functioning. Busch and Lieberman (2010) found that a sample of preschool children who had witnessed DV displayed significantly stronger verbal abilities and perceptual-organizational skills when their mothers had a more secure (or coherent) attachment style. After controlling for maternal education level, maternal coherence of mind on the Adult Attachment Interview (AAI) explained 12% of variance on Performance IQ and 18% of variance on Verbal IQ. Children whose mothers were classified as secure scored 6 points higher on Performance IQ and 8 points higher on Verbal IQ than children of insecure mothers. An earlier meta-analysis based on primarily nonclinical, middle-class samples from 32 studies found a moderate association between infant attachment and children's language ability in the first 3 years of life ($r = .28$) and a smaller but significant association between infant attachment and intelligence ($r = .09$; IJzendoorn, Dijkstra, & Bus, 1995).

Contextual Factors. A recent review concluded that parental sensitivity only explains a small part of the total variation in infant attachment security (Bakermans-Kranenburg, Van IJzendoorn, & Juffer, 2003). Genetic variations may help explain some of the transmission gap in infant attachment security along with many other outcomes. Though we are beginning to understand the interaction between genetics and environment on the impact of attachment and other outcomes, we still have much to learn.

Internalizing and Externalizing Outcomes

A robust body of literature has demonstrated broad associations between childhood abuse and witnessing domestic violence to a range of difficulties in mental and physical health as well as problematic social interactions, additional peer victimization, academic difficulties, problem behaviors, and substance use (Chu and Lieberman, 2010). However, beyond understanding that exposure to traumatic events leads to negative outcomes, we need to understand the mediators and moderators for trajectories of outcomes.

Studies are beginning to examine the mechanisms that lead to the development and maintenance of trauma related symptoms after trauma exposure. For example, Stevens et al. (2013) found that difficulties with emotion regulation, lower social support, and greater exposure to adult interpersonal violence mediated the relationship between childhood abuse (before age 16) and adult PTSD symptoms. The model accounted for 63% of the variance in adult PTS symptoms.

Trauma symptoms are also increasingly seen as a potential mediator or moderator for a host of additional negative outcomes. Scheeringa and colleagues (2005) found that preschoolers with more severe trauma symptoms exhibited greater impairment in functioning in social activities and relationships 2 years later compared with children with less severe trauma symptoms. Trauma symptoms have also been found to mediate the relationship between maltreatment (including witnessing DV) and broadband internalizing and externalizing behaviors in preschoolers (e.g., Miller, Howell, & Graham-Bermann, 2012).

Traumatic expectations may generate hypervigilance and also constrict children's motivation to play, explore, and learn from the physical and interpersonal environment. In a sample of 1-year-old infants from abusive, neglecting, and nonmaltreating low-SES families, infants from abusive families demonstrated less independent and more imitative play than infants from neglecting and nonmaltreating families when observed during mother–child play (Valentino, Cicchetti, Toth, & Rogosch, 2006). At a 15-month follow-up when the children were about 2.5 years of age, these patterns held across groups (Valentino, Cicchetti, Toth, & Rogosch, 2011). Additionally, when examining the development of child play behaviors over time, higher levels of abuse at the initial assessment were associated with lower levels of child-initiated play at the 15-month follow-up.

Age of Onset. Careful specification of the age during which abuse occurs remains important as research is starting to suggest that distinct developmental periods may lead to divergent outcomes. In a sample of 553 children aged 7–13, those who experienced physical or sexual abuse prior to age 5 reported more internalizing symptoms

than children with abuse at later ages or children with no histories of abuse (Cicchetti, Rogosch, Gunnar, & Toth, 2010). Compared with abuse (sexual, physical, emotional) or physical neglect during infancy-toddlerhood (under 3 years of age) or middle childhood, abuse or physical neglect during the preschool years (3–6 years of age) was associated with the most severe externalizing symptoms (Manly, Kim, Rogosch, & Cicchetti, 2001).

Studies with adult samples replicate this pattern. Maercker and colleagues (2004) found in a large representative sample of almost 2,000 women aged 18–45 years that experiencing trauma (as defined by *DSM-IV* criterion A1) prior to age 13 predicted equal risk for depression and posttraumatic stress disorder (PTSD). However, if the trauma occurred after age 13, the risk for developing PTSD became much greater than the risk for depression. Another sample of adults whose age of onset of abuse or neglect was prior to 5 years of age reported higher levels of depressive and anxiety symptoms later in life as compared with individuals with a later age of onset who reported more behavioral problems (Kaplow & Widom, 2007).

These age distinctions also appear to impact development on a cellular level and on brain structures. A study with young adults between the ages of 24 to 32 years indicated that among individuals who had experienced physical abuse, those with onset between ages 3 and 5 years had heightened levels of Epstein-Barr Virus (EBV) antibodies compared with their peers whose onset of physical abuse was during adolescence (Slopen, McLaughlin, Dunn, & Koenen, 2013). EBV antibodies provide an indicator of cell-mediated immune function. Thus, higher levels of EBV antibodies signal the failure of cellular immune processes to impede reactivation of latent viruses. In another study with 26 young adult women aged 18–22 years, hippocampus volume was reduced in association with childhood sexual abuse experienced at ages 3–5 years and ages 11–13 years, and frontal cortex was attenuated in subjects with childhood sexual abuse at ages 14–16 years (Andersen et al., 2008). This is the first study to suggest a differential impact of age at onset of trauma on regional brain volumes. Similarly, Baker and colleagues (2013) found volumetric reductions in the anterior cingulate cortex and insula volumes only for individuals who experienced life stressors (including abuse, neglect, bullying, poverty, divorce, illness, and witnessing domestic violence) between ages 8 and 17 years, compared with individuals who experienced life stressors between ages 0 and 7 years or individuals without any experiences of trauma. These findings represent just the beginning of our understanding on how trauma might disrupt systems of development and bring about cascading effects when the trauma occurs at different time points along the developmental trajectory.

Race/Ethnicity. Any potential racial or other social group differences in the consequences of childhood abuse also remain poorly understood due to limited research on this topic. Lee and colleagues (2012) found that childhood maltreatment led to similar negative consequences for Black and White male youth in adolescence. However, in a sample of Latino women, risk of anxiety disorder was highest for women who had witnessed violence and reported the highest levels of family cultural conflict, providing limited evidence that acculturation moderates the influence of maltreatment on mental health outcomes (Warner, Alegría, & Canino, 2012).

Furthermore, racial discrepancies remain present in the criminal justice system for both juveniles and adults in addition to the child welfare system. For example, Black males are over-represented across all three systems (Fite, Wynn, & Pardini, 2009; Snyder & Sickmund, 2006). Early and severe childhood abuse has been found to be one of the most salient predictors of serious and violent criminal activity in adolescent and young adulthood (e.g., Asberg & Renk, 2013). Additionally, exposure to additional risk factors can further increase the likelihood of delinquent behavior. Some researchers have suggested a differential exposure (increased exposure due to environmental and societal inequalities) as the explanation for the racial disparity; others have put forth a differential sensitivity hypothesis due to exclusionary practices associated with institutionalized racism (see Fite et al., 2009). Overall, findings appear to provide mixed results in support of the differential sensitivity hypothesis. Instead, studies point to differential exposure to a range of risk factors, disparities in access to services, as well as racial biases among authority figures as explanations for the increased representation of non-White youth in the criminal justice system (see Langrehr, 2011). Thus, youth advocates are increasingly calling for competent and sensitive multicultural assessment and treatment in the child welfare and juvenile justice systems.

Sexual Orientation. Childhood emotional abuse showed a stronger association to PTSD and anxiety symptoms for African American individuals identifying as lesbian, gay, or bisexual (LGB) compared with White LGB individuals (Balsam, Lehavot, Beadnell, & Circo, 2010). Similarly, childhood physical abuse showed a stronger relationship with PTSD and anxiety symptoms for Latino LGB participants as compared with White LGB participants. While attention toward race and additional social identity groups is starting to increase across research areas, the impact

of intersecting identities remains an important topic area within the traumatic stress literature.

Caregiving Context. When the child grows up in the context of violence, traumatic expectations become the norm as the child learns to anticipate repeated and unrelieved pain and fear. When exposed to simulated adult conflict, infants under 1 year of age whose mothers reported experiencing domestic violence (DV) displayed more facial expressions of distress than infants whose mothers did not reported experiences of DV (DeJonghe, Bogat, Levendosky, von Eye, & Davidson, 2005). This finding suggests that infants exposed to DV may have a heightened sensitivity to adult verbal conflict.

The negative impact of exposure to parental conflict can manifest very early in life. In a sample of 6-month-old infants, higher levels of exposure to parental conflict was found to be associated with greater stress reactivity as measured by greater withdrawal of vagal tone during a laboratory stressor task (Moore, 2010). A functional magnetic resonance imaging study with a sample of healthy infants aged 6 to 12 months examined the association of parental conflict with neural responses to angry auditory input during natural sleep (Graham, Fisher, & Pfeifer, 2013). Results showed greater activation in brain regions associated with emotion and stress reactivity/regulation (e.g., rostral anterior cingulate cortex, caudate, thalamus, hypothalamus) for infants whose mothers reported higher levels of parental conflict.

Negative parenting practices can also significantly influence children's responses to traumatic events. For example, corporal punishment has been shown to be consistently linked with a range of negative child outcomes including aggression, lower levels of moral internalization, mental health, delinquent and antisocial behavior, and lower parent–child relationship quality (Gershoff, 2002). A longitudinal birth cohort of almost 2,000 children from 20 U.S. cities found that maternal spanking at age 5 predicted higher levels of child externalizing behavior at age 9, as compared with children who did not experience maternal spanking (MacKenzie, Nicklas, Waldfogel, & Brooks-Gunn, 2013). Paternal spanking at age 5 also predicted lower receptive vocabulary at age 9.

However, corporate punishment as a parenting practice remains a controversial practice with a sizeable portion of adults still in favor of this parenting practice (Bell & Romano, 2012). MackKenzie and colleagues found that 57% of mothers and 40% of fathers utilized spanking when the children were 3 years of age, while 52% of mothers and 33% of fathers spanked their children when the children were 5 years of age (MacKenzie et al., 2013). Some parenting advocates point out that corporal punishment may be a possible precursor to physical abuse given the unclear boundary between acceptable corporal punishment and physical abuse. Yet others suggest that the association between corporal punishment and negative outcomes may be due to third variables such as inconsistent parenting and parental stress; thus corporal punishment in of itself may not be a cause of negative outcomes (Gershoff, 2002).

Posttraumatic Stress Disorder

One of the most commonly examined outcomes of trauma exposure is posttraumatic stress disorder (PTSD). The recently released fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders,* (*DSM-5;* American Psychiatric Association, 2013) states that the essential feature of PTSD is the development of characteristics symptoms following exposure to an extreme traumatic stressor (criterion A1). Notably, the previous edition had included an A2 criterion of experiencing fear, helplessness, or horror as part of the traumatic event. The *DSM-5* no longer includes the A2 criterion because research suggested that this criterion did not improve diagnostic accuracy (Friedman, Resick, Bryant, & Brewin, 2011). The characteristic symptoms that were categorized into three clusters in the previous edition has been recategorized into four clusters: reexperiencing of the traumatic event (criterion B), avoidance of stimuli associated with the trauma and numbing of general responsiveness (criterion C), negative alterations in cognitions and mood (criterion D), and increased arousal (criterion E).Within each criterion, specific symptoms are described, and a logarithm is provided to determine whether the person meets the following criteria for diagnosis: at least one symptom from criterion B (reexperiencing), at least one symptom from criterion C (avoidance), at least two symptoms from criterion D (negative alterations in cognitions and mood), and at least two symptoms from criterion D (arousal). The full-symptom picture must be present for longer than 1 month (criterion F), the disturbance must cause clinically significant distress or impairment in important areas of functioning, such as work or social relations (criterion G), and the disturbance is not due to medication, substance use, or other illnesses.

There is wide recognition that the previous *DSM-IV* criteria for PTSD lacked developmentally informed considerations for infants, toddlers, and preschoolers. Scheeringa and colleagues (2003) compared 62 traumatized preschool children to 63 nontraumatized preschool children, all aged 20 months through 6 years. The children were recruited

from the community, including clinics, shelters, an intensive care inpatient unit of a level 1 trauma center, and a Head Start center. Parents reported on their children's symptoms. Findings showed that none of the traumatized children met the criteria for PTSD based on the *DSM-IV* (Scheeringa, Zeanah, Myers, & Putnam, 2003). However, when using an alternative criteria algorithm of one cluster B (reexperiencing) symptom, one cluster C (avoidance/numbing) symptom, two cluster D (arousal) symptoms, and four novel symptoms, they diagnosed PTSD at a rate of 26% in the same group of children. Using the revised algorithm, the group of children who were diagnosed with PTSD had significantly more comorbid symptoms (separation anxiety disorder; oppositional defiant disorder; major depressive disorder; attention-deficit/hyperactivity disorder; as well as general internalizing, externalizing, and total problems) when compared with children in the trauma/no-PTSD group or the no-trauma group.

Scheeringa and colleagues (2005) then reexamined these children's functioning one and two years following the initial time point and obtained information on community treatment. They found that those children initially diagnosed with PTSD at time 1 (from Scheeringa et al. 2003) showed significantly more PTSD symptoms and functional impairment in more domains over the course of 2 years than did children without PTSD. Children with PTSD symptoms did not show decreases in symptom levels over 2 years, even with community treatment. Specifically, avoidance/ numbing symptoms increased over time (particularly at 1-year follow-up), whereas reexperiencing symptoms decreased over time. Together, these findings argue for lowering the cluster C (avoidance/ numbing) symptom threshold criteria for younger children while keeping cluster B (reexperiencing) and D (arousal) symptom threshold criteria the same.

This alternative algorithm was further supported by a recent review which found that very few young children (0–5%) met the avoidance/numbing symptom cluster using the *DSM-IV* three-symptom threshold; however, when the threshold was reduced to one symptom, rates increased to 18–62% (De Young, Kenardy, & Cobham, 2011). Notably, reexperiencing was the most commonly endorsed symptom cluster in young children, with rates ranging from 35 to 80% followed by hyperarousal (32–45%). In fact, prevalence rates of PTSD in young children varied from 6.5% to 60% when using the alternative PTSD algorithm, depending on the type of trauma, time of assessment posttrauma, and type of sample. De Young and colleagues noted that if the *DSM-IV* criteria had been used for the PTSD diagnosis, prevalence rates would have been substantially lower.

Thus, to meet the specific needs of children aged birth to five, *Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood* (*DC:0–3* and *DC:0–3R*) was created by Zero to Three: National Center for Infants, Toddlers and Families (Zero to Three, 1994, 2005). The diagnostic criteria for PTSD in the *DC:0–3R* manual specifically reflect the developmental manifestations of traumatic stress in the first 5 years of life. The criteria are written to conform to the algorithm initially proposed by Scheeringa and colleagues: at least one reexperiencing symptom (posttraumatic play, recurrent and intrusive recollections of the traumatic event outside play, repeated nightmares, physiological distress, and episodes of flashbacks or dissociation), at least two hyperarousal symptoms (sleep problems, concentration problems, hypervigilance, exaggerated startle response, irritability/anger), and at least one numbing of responsiveness or interference with developmental progress symptom (increased social withdrawal, restricted range of affect, markedly diminished interest or participation in significant activities, and efforts to avoid trauma reminders). The diagnostic criteria also include associated symptoms (regression of developmental skills, new aggression, new fears, and inappropriate sexual behaviors). This pattern of symptoms should last for at least 1 month.

Prior to the release of *DSM-5*, Scheeringa and colleagues (2012) assessed for diagnosis of PTSD using four diagnostic criteria sets in a sample of 284 3- to 6-year-old trauma-exposed children: *DSM-IV*, PTSD-alternative algorithm, *DSM-5* proposed criteria, and *DSM-5* criteria with 2 additional symptoms. The *DSM-IV* criteria resulted in the lowest rate (13%) of diagnosis out of the four. The PTSD-Alternative Algorithm yielded 45% of PTSD diagnoses while the *DSM-5* proposed set resulted in 44%. Using the *DSM-5* criteria with 2 additional symptoms, the rate of PTSD was at 49%. The three alternative criteria sets to *DSM-IV* showed high agreement on the presence of diagnoses (100%) but low agreement on the absence of diagnoses (58–64%). The authors suggested that these findings lend support to a developmental subtype for PTSD.

Consistent with research in the last two decades with young children, the *DSM-5* now includes a preschool subtype for PTSD in children who are 6 years or younger (American Psychiatric Association, 2013). The criteria for the preschool subtype are more behaviorally anchored and developmentally sensitive to detect PTSD in young children. The reexperiencing and arousal symptom clusters remain largely similar to the set of PTSD criteria in adults. The major changes are in the avoidance and

negative cognition/mood symptom clusters where symptom descriptions were modified to enhance face validity and the symptom threshold is now one symptom in either the avoidance cluster or the negative cognition/mood cluster (which is a decrease from the previous threshold of three symptoms in the avoidance cluster).

Caregiving Context. Several models have been proposed to explicate the intergenerational transmission of psychopathology from parent to child. Scheeringa & Zeanah (2001) propose a relational PTSD model where caregiver's responses to the traumatic stressor can have several types of effect on the young child. The moderating effect suggests that the degree to which the caregiver can accurately read the child's cues and respond effectively to the child's needs may intensify or reduce the adverse effect of the trauma event on the child's symptoms. The vicarious traumatization effect suggests that if a caregiver's responsiveness to the child is affected by a traumatic event that the child did not experience directly, the impact of the trauma on the caregiver–child relationship accounts for the effect of the trauma on the child's symptoms. The compound effect suggests that when both caregiver and child are exposed to trauma, the posttraumatic symptomatology in one partner exacerbates the symptoms of the other.

Lyons-Ruth and colleagues (1999) proposed a relationship diathesis model where vulnerability to stress-related dysfunction is determined by at least three factors: the characteristics of the stressor, the individual's genetic vulnerability to stress, and the capacity of the attachment system to modulate the high levels of arousal that accompany stress. In this model, children respond with emotional and behavioral symptoms either when the stressor is too overwhelming or when the attachment relationship is unable to modulate the child's intensely negative affective response.

Extensive empirical evidence supports these theoretical pathways linking the child's traumatic stress responses with parental stress, particularly with parental depression, PTSD, separation, and insecure attachment. A sample of preschool children exposed to the September 11th attacks and their mothers were recruited to examine children's behavioral problems as measured by mother and preschool teacher report (Chemtob et al., 2010). Children of mothers with both depression and PTSD had the highest rate of clinically significant behavior problems compared with children of mothers with only depression or mothers with neither disorder, as rated by both mothers and preschool teachers. Children of mothers with depression and PTSD also exhibited a larger number of behavior problem clusters. Crusto and colleagues (2010) also found that parenting stress partially mediated the relationship between family violence and trauma exposure and posttraumtic stress symptoms. Additional negative outcomes for young children with depressed mothers include increased parent–child conflict, behavioral problems, and peer relationship difficulties (for a review, see Markese, 2011).

While the majority of research focuses on the impact of negative or adverse caregiving environments, there is minimal research on whether the impact of early trauma can be reversed with a nurturing caregiving environment. One of the exceptions is a recent study found that 34 5–12-year-old children placed into the child welfare system due to abuse or neglect and reactive attachment disorder who were adopted into well-functioning families exhibited typical profiles of cortisol secretion (Kocovska et al., 2013).

Methodological Issues

To date, most studies on the impact of childhood trauma tend to examine either broadband maltreatment (i.e., collapsing all types of abuse and neglect together) or to compare the absence versus presence of a specific type of traumatic event. For example, a longitudinal study following a large cohort of approximately 2,700 sexually abused children over 43 years using a public psychiatric database found that childhood sexual abuse is a substantial risk factor for developing a range of mental disorders (Cutajar et al., 2010). However, this study did not examine children with other types of abuse as a comparison group or as a comorbid condition.

More recent studies are beginning to suggest that outcome patterns may vary by abuse type and we should begin examining profiles of abuse and neglect. Pears and colleagues (2008) examined profiles of abuse and neglect in 117 preschool-age foster children. In terms of outcome, the profile with sexual abuse had higher cognitive functioning as compared with other profiles (supervisory neglect; physical abuse; or sexual and physical abuse). However, this profile also had the highest level of externalizing problems. Internalizing problems was associated with three profiles: physical abuse; sexual abuse; or both sexual and physical abuse (Pears, Kim, & Fisher, 2008). Another study with a community sample of 2–3-year-old children exposed to different types of violence found that interpersonal violence exposure was associated with symptoms of depression, anxiety, posttraumatic stress disorder, and disruptive behavior while potentially traumatic exposure that were noninterpersonal in nature was primarily associated with phobic anxiety (Briggs-Gowan et al., 2010).

Another often-cited criticism of trauma research is the lack of experimental designs, where randomization cannot be done due to ethical reasons. Therefore, causality is often approximated from limited longitudinal designs. One methodology to better assess causality without utilizing a true experimental design involves propensity score matching (Rosenbaum & Rubin, 1983). The propensity score is the conditional probability of assignment to a treatment condition based on a range of covariates. Individuals are matched based on similar propensities and compared based on the treatment condition of interest. Causal inferences can be made using this methodology because propensity score matching balances all observed covariates prior to estimating treatment effects, thereby controlling for pretreatment selection bias.

Utilizing this methodology, a recent study examined the causal impact of childhood-limited maltreatment and adolescent maltreatment on early adult adjustment (Thornberry, Henry, Ireland, & Smith, 2010). The findings demonstrated that childhood-limited maltreatment was significantly related to drug use, depressive symptoms, and suicidal thoughts, which the authors characterized as internalizing problems. Adolescent maltreatment was significantly related to a broader range of outcomes including criminal activities, alcohol and drug use, risky sexual behaviors, and suicidal thoughts. Because of the propensity score matching, the authors were able to conclude that maltreatment was not merely a risk factor for these later outcomes but that it acted as a causal agent. As the field moves toward more complex approaches, researchers are able to start answering the questions of why, how, and under what conditions does trauma exposure lead to maladaptive outcomes.

ENVIRONMENTAL INTERVENTIONS

Prevention

In an earlier section we reviewed various risk factors for exposure to child abuse at different ecological levels (e.g., individual, family, societal). Identifying risk factors is important and valuable for prevention; to date, most prevention programs target the risk factor of parenting practices. A meta-analysis of 40 different early prevention programs for families with young children (0 to 3 years old) at risk for physical child abuse and neglect showed a treatment effect size of 0.29 (Geeraert et al., 2004). The programs, mostly with nonrandomized designs, showed significant decreases in abusive and neglectful parenting and increases in child functioning, parent–child interaction, parent functioning, and family functioning. Another review of 15 studies on 14 different prevention programs for children ages birth to 5 years indicated an effect size of 2.9% reduction post program participation, which equals a 31% reduction in actual maltreatment rates (Reynolds, Mathieson, & Topitzes, 2009). The authors noted that common elements of the programs showing effectiveness included implementation of curriculum by professional staff, high dosage and intensity of sessions, and comprehensiveness on scope of program content.

Other than parenting practices, we still know little about ways to prevent childhood abuse. In general, finding methods to study protective factors that keep children safe from abuse remains a challenge. The cross sectional nature of this research means that we know little about how risk or protective factors change over time. This is particularly important considering the tremendous cognitive, emotional, and social development that occurs across the first 18 years of life. Also, protective factors are often simply the flip side of identified vulnerability factors; for example, if female gender is a risk factor, then male gender is protective. We therefore still know little about protective factors independent of risk for experiencing childhood abuse. Further, most programs currently involve treatments to ameliorate the effects of trauma on childhood development and functioning versus prevention of childhood maltreatment.

Resilience

Resilience is typically thought of as the ability to function adaptively after experiencing an adverse or traumatic event. Though specific operationalization differs across studies, three main types of psychosocial protective factors for promoting resilience in children have emerged, similar to the risk factors reviewed above. Findings show that individual characteristics (e.g., intellectual functioning, self-regulation skills, temperament, personality), nurturing family environment (e.g., positive connections with adults, maternal warmth), and broader contextual variables (e.g., positive social support) all help facilitate positive adaptation in the face of adversity or trauma (see Masten, 2001).

Cicchetti and colleagues have noted that the majority of research on resilience to date has primarily focused on single-level analyses of psychosocial processes (Cicchetti, 2013; Curtis & Cicchetti, 2003). Studies with multilevel analyses focusing on the interaction of biological, genetic, and psychological systems are just beginning to add to our knowledge base regarding resilience. For example, Curtis and Cicchetti (2007) found that there was greater

electroencephalogram (EEG) activity in the left hemisphere of children who showed more resilience. Lower morning cortisol was found to be related to higher resiliency in nonmaltreated children while higher morning cortisol was related to higher resiliency in physically abused children (Cicchetti & Rogosch, 2007). Additionally, maltreated children with high resiliency exhibited an atypical rise in dehydroepiandrosterone (DHEA) levels from morning to afternoon.

Sapienza and Masten (2011) similarly described four waves of research regarding resilience. The first wave focused on descriptive data to figure out what makes a difference in increasing resilience. The second wave shifted to the process of how resilience functions. The third wave promoted resilience through interventions. Currently, in the fourth wave, researchers are adapting the developmental cascades model to examine the processes of interaction across system levels that influence individual development within the larger context. The fourth wave has been informed by multiple areas of research, such as the gene x environment interaction, epigenetic processes, and differential susceptibility (e.g., Cicchetti & Rogosch, 2012). As these studies continue to advance our understanding of resilience, it remains important to translate that knowledge into targeted and timely efficacious preventions and interventions.

Treatment

The Agency for Healthcare Research and Quality initiated the Effective Health Care Program in 2005 to provide reviews on the comparative effectiveness of different medical interventions to help consumers and providers to make informed choices among different treatment options. Two reports were completed recently to review clinical interventions for children exposed to traumatic experiences. The first review included 24 clinical trials and one cohort study testing interventions for children ages birth to 14 years who have specifically experienced abuse or neglect (Goldman Fraser et al., 2013). The report concluded that although there were a number of promising intervention programs addressing child outcomes after exposure to maltreatment, there was generally insufficient or low strength of evidence to draw firm conclusions regarding efficacy or effectiveness due to small sample sizes or only one or two trials for each intervention. No studies on pharmacotherapy met eligibility criteria to be included in the review. The report also noted various gaps in the literature. There were no studies that compared the efficacy or effectiveness of interventions with different characteristics (e.g., setting, service delivery format, theoretical orientation). The authors were unable to identify any studies that addressed race or ethnicity variables. Intervention studies also did not examine dosage effects—in other words, how many sessions of an intervention is needed to produce change—or impact of maltreatment characteristics (e.g., severity, chronicity, timing) on treatment outcome.

The second report reviewed interventions for children ages birth to 17 years who were exposed to traumatic events other than child maltreatment or family violence (Forman-Hoffman et al., 2013). The report included 21 clinical trials and one observational study that evaluated 19 different interventions. The authors found that some psychotherapy treatments were promising, particularly programs with elements of cognitive behavioral therapy which showed good effect sizes. However, there was again generally low strength of evidence to draw firm conclusions due to small sample sizes or only one or two trials for each intervention. Importantly, no studies attempted to replicate findings of effective interventions. Also, no pharmacotherapy intervention showed effectiveness in outcomes. Although both comparative effectiveness reviews pointed out gaps in the literature and noted that the field is still in its infancy, a number of interventions do show benefits for children exposed to abuse. We highlight some of those interventions below.

Infant–Parent Psychotherapy. Cicchetti, Rogosch, and Toth (2006) also compared a similar relationship-based therapy with infants, infant–parent psychotherapy (IPP), with a psychoeducational parenting intervention (PPI) and community standard (CS) controls who received usual standard of care under Department of Human Services management, all administered to maltreated children. These groups were compared with a normative comparison group with nonmaltreating families. At baseline, mothers in the maltreatment groups reported having experienced more abuse and neglect in their own childhoods, more negative representations of their childhood, and more negative relationships with their own mothers currently as compared with the mothers in the nonmaltreatment group. They also reported less availability of social support from family members, higher current parenting stress, less parenting competence, more social isolation, more health concerns, and less understanding of appropriate parenting attitudes and practices. During mother–child observations, the mothers from the maltreatment groups also demonstrated lower sensitivity in interactions with their infants. Infants in maltreating families exhibited significantly higher rates of insecure attachment with their

mothers, and only one infant (<1%) was classified as securely attached. In contrast, the rate of secure attachment for infants in nonmaltreating families was 32.7%. At postintervention, the rate of secure attachment increased significantly in the two intervention groups (IPP and PPI) to 60.7% and 54.5%, respectively. In comparison, the rate of secure attachment in the CS group remained low (1.9%). Furthermore, the rate of secure attachment in the normative comparison group remained at 38.6%, which was also significantly higher than the CS group.

Child–Parent Psychotherapy. Child–parent psychotherapy (CPP) is a relationship-based intervention grounded in psychoanalytic, attachment, and trauma theory that also includes social learning and cognitive behavioral intervention strategies as vehicles for change (Lieberman & Van Horn 2005, 2008). Because young children organize their responses to stress and danger around their caregiving relationships, CPP is organized around the premises that young children turn preferentially to their parents or primary caregivers for protection and safety and that trauma shatters the child's perception of the parent as a competent and reliable protector. Using the format of joint child–parent sessions, CPP therapists help to translate the emotional meaning of behaviors between the parent and the child, enabling them to co-construct a trauma narrative that holds developmentally appropriate meaning for both partners.

In a number of studies, CPP as an attachment theory informed intervention has shown efficacy in improving secure attachment and reducing rates of disorganized attachment (e.g., Cicchetti et al., 2006; Lieberman, Weston, & Pawl, 1991; Lieberman, Van Horn, & Ippen, 2005; Lieberman, Ippen, & Van Horn, 2006; Stronach, Toth, Rogosch, & Cicchetti, 2013). For example, in a randomized controlled trial comparing CPP to case management plus community intervention as usual, CPP was significantly more effective than the control group treatment in reducing (1) children's behavior problems and PTSD symptoms and (2) mothers' symptoms of avoidance (Lieberman et al., 2005).

When examining treatment effectiveness for children's level of trauma exposure, results indicated that children at high risk exposure as well as low risk exposure demonstrated improvements in symptoms (Ippen, Harris, Van Horn, & Lieberman, 2011). Specifically, children who reported four or more adverse childhood events who participated in CPP reported greater reductions in PTSD and depression symptoms as compared with children in a control condition. Children who reported four or less adverse childhood events who participated in CPP reported greater reductions in PTSD symptoms as compared with children in a control condition.

The impact of CPP on secure attachment and child behaviors appear to maintain over time. In one 6-month follow-up study, changes in child behavior problems were sustained posttreatment (Lieberman, Ippen, & Van Horn, 2006). PTSD symptoms were not measured at the 6-month follow-up for either mother or child, but general functioning continued to improve in mothers who received CPP whereas functioning of the mothers in the comparison group did not. In another 1-year follow-up study, toddlers in the CPP group had higher rates of secure attachment and lower rates of disorganized attachment as compared with children in a comparison parenting intervention or community standard intervention group (Pickreign Stronach et al., 2013). Thus, early intervention appears to be effective in promoting and sustaining secure attachment over time.

Attachment and Biobehavioral Catch-up. Attachment and Biobehavioral Catch-up (ABC) is a 10-session manualized intervention that targets three core issues for young foster children (Dozier, Higley, Albus, & Nutter, 2002). First, children in foster care often regulate physiology and behavior differently than do other children (Dozier et al., 2006). Young children in foster care often behave in ways that push new caregivers away. Third, foster parents' own issues sometimes create difficulties in providing nurturance. Whereas birth children can often cope effectively with nonnurturing care, children in foster care often develop disorganized attachments to nonnurturing caregivers, which in turn puts them at risk for a number of problematic outcomes. ABC helps foster parents create an environment that enhances regulatory capabilities. Various components of the intervention help caregivers to (*a*) follow the child's lead, (*b*) appreciate the value of physical contact with their child, (*c*) create conditions that allow their child to express, recognize, and understand emotions, and (*d*) provide nurturing care. Sessions include psychoeducation, discussions, and interactions between the foster parent and child.

Dozier and colleagues (2006) examined preliminary data from the first 60 children who were randomly assigned to receive the ABC treatment or an educational comparison intervention (Developmental Education for Families, which targets cognitive development) and an additional 104 children in a nonfoster care control group. At 1-month posttreatment, children whose foster caregiver received the ABC intervention showed a.m. and p.m. cortisol levels

comparable to the nonfoster care group. Children whose foster caregiver received the control intervention displayed higher-than-typical levels of cortisol across the day. For children in the ABC intervention group, older children (18–36 months) had lower problem behaviors based on parent report as compared with younger children (0–17 months). Children in the intervention group also showed stronger cognitive flexibility and theory of mind skills than children who received the control intervention; the intervention group was similar to comparison group of children who were never in foster care (Lewis-Morrarty, Dozier, Bernard, Terracciano, & Moore, 2012).

Multidimensional Treatment Foster Care Program. The Multidimensional Treatment Foster Care Program (MTFC) is a multicomponent program where foster parents complete intensive training prior to placement. In the preschool version, the Multidimensional Treatment Foster Care Program for Preschoolers (MTFC-P; Fisher, Ellis, & Chamberlain, 1999), foster parents first complete an intensive 12-hour training. After child placement, they receive daily telephone calls with a consultant who provides support and supervision, weekly support groups, and 24-hour on-call access. Children receive services from a behavior specialist and attend weekly therapeutic play-group sessions. If possible, a family therapist works with birth parents or additional adult caregivers to familiarize them with parenting skills. These services last for 6 to 12 months, including any transition periods to a permanent placement.

Fisher and Kim (2007) examined results in a randomized trial of the MTFC-P over a 12-month period after a new foster care placement. Fifty-seven children who participated in the intervention showed significant increases in secure behavior and decreases in avoidant behavior as compared with 60 children in the control condition who received foster care services as usual (Fisher & Kim, 2007). Both groups showed significant decreases in resistant behavior over 12 months. For participants in MTFC-P, children who entered foster care at older ages experienced greater increases in secure behavior over time compared with children in the control condition, who showed the opposite pattern. Preschool children who received the intervention also exhibited cortisol activity that became comparable over time to a comparison nonmaltreated community sample from low-income families (Fisher, Stoolmiller, Gunnar, & Burraston, 2007). Children in foster care who did not receive the intervention exhibited increasingly flattened morning-to-evening cortisol activity over time. Fisher and Stoolmiller (2008) found that foster parents who received the intervention reported a significant decrease in parenting stress related to child problem behavior compared with an increase in caregiver stress in foster parents who were in the control condition. Intervention also decreased the permanent placement failure rate and mitigated the effects of multiple foster placement on risk for permanent placement failure (Fisher, Burraston, & Pears, 2005).

The Multidimensional Treatment Foster Care for Adolescents (MTFC-A; Chamberlain, 2003) version has also shown positive outcomes for adolescents in foster care. In MTFC-A, foster care parents are also intensively trained, supervised, and supported similar to the preschool version on ways to provide positive adult support and mentoring, close supervision, and consistent limit setting. Youth placed in the specialized foster family also receive in-home services and peer as well as educational support. Results from multiple trials show effectiveness in reducing arrest rates and deviant peer affiliations, placement disruption, pregnancy rates, and externalizing as well as internalizing behaviors (for a review, see Leve et al., 2012).

Multisystemic Therapy for Child Abuse and Neglect (MST-CAN; Swenson, Penman, Henggeler, & Rowland, 2010) was adapted from the standard Multisystemic Therapy (MST; Henggeler, Schoenwald, Borduin, Rowland, & Cunningham, 2009). MST-CAN utilizes a recursive process to identify, develop, and prioritize interventions based on the needs of each family. The first phase is focused on assessing the goals, strengths, and needs of each family across each ecological level (e.g., individual, peers, family, school). Then target behaviors are identified across these systems and interventions designed using empirically supported treatment methods to improve the target behaviors. If target behaviors do not improve, the assessment is conducted again in an iterative process until the desired outcomes are achieved. Given the outcome based approach, treatment length varies by each family's needs. As part of MST-CAN, the treatment team works closely with child protective services (CPS) to foster interactions between the family and the CPS system as well as to ensure CPS decision making based on clinical needs or progress. Parents also received treatment for their own trauma-related symptoms if appropriate.

MST has been utilized widely in many communities, primarily for substance use and antisocial behaviors, and has shown efficacious and effective outcomes (Henggeler et al., 2009). A randomized effectiveness trial on MST-CAN with children who have experienced physical abuse also demonstrated that MST-CAN was significantly more effective than outpatient treatment in reducing mental

health symptoms, parent psychiatric distress, maladaptive parenting behaviors, and youth placements (Swenson, Schaeffer, Henggeler, Faldowski, & Mayhew, 2010).

Trauma-Focused Cognitive Behavioral Therapy. Cohen & Mannarino (2008) described an evidence-based treatment, trauma-focused cognitive behavioral therapy (TF-CBT), for parents and traumatized children. This particular intervention provides children and parents with stress management skills prior to the processing of children's traumatic experiences together. A particular strength of this study was the documented feasibility of treatment in terms of the frequency by which children understood concepts given the young age of the children and concerns of their level of understanding. However, a limitation of the study was the high attrition rate. Although additional outcome studies are needed to further establish effectiveness of this treatment, it has been designated the treatment with the best established efficacy (e.g., Chadwick Center for Children and Families & Child and Adolescent Services Research Center, 2009) and has been disseminated on a large scale.

Resilient Peer Treatment. Fantuzzo and colleagues (2005) tested the effectiveness of Resilient Peer Treatment, a peer-mediated classroom-based intervention for socially withdrawn preschool children with a history of maltreatment. Resilient Peer Treatment involved 15 play sessions (three per week) over a 2-month period. The target child was paired up with a play buddy in the same classroom who was coached by a play supporter in positive play interactions with the target child. Eighty-two socially withdrawn children, with and without histories of maltreatment, were randomly assigned to resilient peer treatment or attention-control interventions. Teacher report and observational coding indicated that treatment led to higher levels of collaborative peer play interactions as compared with the control intervention. This treatment effect was present for both maltreated and nonmaltreated children.

Intervention Impact on Neurobiology

In addition to psychosocial outcomes, recently published studies with children exposed to traumatic stress show that intervention programs also have a positive impact on biological functioning. Specifically, HPA functioning has shown improvement after short-term interventions, particularly with regard to the diurnal rhythm in cortisol production (Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Fisher, Stoolmiller, Gunnar, & Burraston, 2007). Cicchetti and colleagues found in a sample of 1-year-old infants that morning cortisol levels for maltreated infants receiving child–parent psychotherapy or psychoeducational parenting intervention became indistinguishable from nonmaltreated infants while a control group of maltreated infants receiving standard community services showed progressively lower levels of morning cortisol (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011). This group difference first appeared at mid-intervention and was maintained at 1-year postintervention when the infants were approximately 3 years of age.

Importantly, research is beginning to show evidence that there are genetic and biologically based sensitivities to intervention. Infants who scored relatively high on irritability as newborns showed more benefits from a security-promoting intervention compared with infants who scored low on irritability (Cassidy, Woodhouse, Sherman, Stupica, & Lejuez, 2011). An intervention for children with disruptive behavior disorder was effective only for those displaying high cortisol reactivity (Van De Wiel, Van Goozen, Matthys, Snoek, & Van Engeland, 2004).

A randomized control trial found that an attachment-based parenting intervention (Video-Feedback Intervention to Promote Positive Parenting and Sensitive Discipline) with 1- to 3-year-old toddlers is most effective at reducing externalizing behaviors and daily cortisol production for children with the DRD4 7-repeat polymorphism (Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman & Juffer, 2008; Bakermans-Kranenburg, Van IJzendoorn, Mesman, Alink, & Juffer, 2008). Other studies have shown similar treatment responsiveness in children with the DRD4 7-repeate allele (e.g., Beach, Brody, Lei, & Philibert, 2010; Kegel, Bus, & Van IJzendoorn, 2011).

Van den Hoofdakker and colleagues (2012) found that a behavioral parenting training intervention produced greater treatment effects on ADHD behaviors in children (aged 4–12) with zero or one copies of the DAT1 dopamine transporter gene 10-repeat allele as compared with a control condition. However, the same intervention did not produce any significant treatment effects in children with two copies of the DAT1 10-repeat alleles.

These findings all point to a differential susceptibility model where children with certain genetic predispositions show particular benefit from positive contexts. However, the mechanisms underlying these associations and the differential susceptibility model remain unclear. One line of research is beginning to explore potential explanations for the link between genetic predispositions and differential susceptibility to interventions. Hayden and colleagues (2008) compared nondepressed and depressed 7-year-old children's reactions to sad movies or a sad

imaginary scenario. Children with the ss allele genotype of the 5-HTT gene had more negative self-referential responses to the tasks. Since depression is associated with negative information processing as well as increased activity in the amygdala, the authors surmised that the genetic predisposition for heightened activity in the amygdala may be responsible for the negative cognitive distortions so common in depression (Beck, 2008). In support of this hypothesis, Eley and colleagues (2012) also documented intervention benefits restricted to short allele carriers of the 5-HTT gene.

CONCLUSION

Policy

Estimates show that more than 90% of public sector service systems for children and families do not deliver evidence-based practices (Garland, Landsverk, Hough, & Ellis-Macleod, 1996; Landsverk, Garland, & Leslie, 2002). A National Child Traumatic Stress Network (NCTSN) descriptive study indicated that children who experienced at least one type of traumatic event were involved with many different kinds of systems that provide services for children, including social services, school-based services, juvenile justice, health, and mental health (Briggs et al., 2013). The authors noted that the pervasiveness of trauma exposure across various child service systems point to the need for all child service systems to become more trauma informed, to conduct comprehensive screenings for trauma histories, and for cross-system coordination. Thus, further training and dissemination of evidenced-based practices is warranted.

Future Directions

Recently, the Agency for healthcare Research and Quality commissioned a set of systematic reviews to provide comprehensive information on the effectiveness and safety of clinical interventions. Two separate reports on interventions that address trauma-related symptoms in children and adolescents concluded that there was preliminary support for a number of interventions which were beneficial relative to no treatment. However, most of the studies showed low strength of evidence due to small samples and methodological limitations; far more research is also needed to demonstrate comparative effectiveness of interventions (Goldman et al., 2013; Forman-Hoffman et al., 2013).

The studies reviewed here point to several important policy issues related to child welfare practices. For example, continued training is needed for professionals who interact with children and families across a range of settings, such as in the medical system, to recognize and assess maltreatment based on cutting edge research on vulnerability and protective factors. Researchers such as Hibbard and Desch (2007) have noted that many health workers do not receive sufficient training on the identification of certain risk factors, such as disabilities, for child abuse and neglect.

Because the literature on vulnerability and protective factors has been anything but static, trainings must be updated as the research literature advances. As new research emerges, we continue to identify additional vulnerability and protective factors as well as complex interactions among those factors. Training professionals to identify children who are at risk for abuse or who have been abused must, therefore, capture the complex relationship between risk factors. For example, it would be an unwelcome outcome if data on ethnicity and abuse led to focused attention on certain subgroups without considering the interaction between ethnic identity and other vulnerability/protective factors to understand the risk across and within various groups.

With up-to-date training, health care providers and other professionals will be in a unique position to use their knowledge to identify maltreated children as well as educate parents and families on ways to protect their children. To the latter point, we urgently need to learn to better use this body of research for risk assessment to prevent maltreatment from occurring, which will have to involve both policy and research agendas. For example, we need rigorous research methods to examine whether the vulnerability and protective factors identified in samples that rely on documented abuse reflect actually underlying differences (e.g., between groups) versus biases in the system.

Additionally, prevention of maltreatment requires programs to systematically and comprehensively address multiple risk and protective factors, including the family and surrounding community (Herrenkohl et al., 2008). While we have recommended that future research target multiple levels of influence on maltreatment, so too should policy-makers address the implications of multiple system interactions. For example, mothers who are victimized by their partners may not be able to fully protect their children because leaving the abusive partner may also result in loss of their economic means of support or increased safety risks to mothers and children. While insuring the safety

of children is paramount, policies can help to strengthen communities to support families and to reduce prevalence of child maltreatment (Coulton et al., 2007). Community social support appears to be an especially important protective factor that warrants further research to identify specific policies that can build this capacity to decrease child abuse risk.

Furthermore, a more collaborative team-approach response will help future data collection and provide more comprehensive responses to children who have experienced maltreatment. For example, because there is no federal mandate that information be collected on families involved in multiple systems (e.g., a family with identified child abuse that is also engaged in mandated substance treatment), the information available on how risk and protective factors interact are largely estimates based on an interpolation of research studies. Future studies should establish accurate estimates of families who access multiple systems to more fully assess the need for services, and in turn develop appropriate service capacity to respond to that need. In particular, states and communities need to fully understand the size, scope, and extent of the issue of families who are involved in systems in their jurisdictions as these factors may also vary depending on geographic locations and neighborhood characteristics. In sum, researchers and policy makers must work together to provide comprehensive and collaborative services in both the prevention and treatment of child maltreatment.

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CHAPTER 11

Child Maltreatment and Developmental Psychopathology: A Multilevel Perspective

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INTRODUCTION

In this chapter, we infuse a *developmental psychopathology* perspective into our understanding of the sequelae of maltreatment. Specifically, we highlight the importance of employing a *multilevel perspective* when examining aspects of socio-emotional, cognitive, psychophysiological, neurobiological, and genetic functioning. Utilizing a developmental lens we discuss: affect differentiation and emotion regulation, emotion recognition, attachment, the development of an autonomous self, peer relationships, adaptation to school, memory, and personality organization and psychopathology. We also present findings on gene–environment interaction (GxE) and epigenetics, neuroendocrine functioning, physical health outcomes, and neurobiological development. Studies elucidating resilience despite caregiving adversity also are presented. We then address methodological issues in maltreatment research and the translation of research into *prevention*, *intervention*, and *social policy* arenas. We conclude by directing our attention to necessary next steps to foster work in this area. We highlight advances in research that are likely to increase our understanding of the effects of *child maltreatment* across the life course. We also recommend strategies for fostering advances and addressing challenges that have and will continue to accompany investigations into this all too pervasive societal problem.

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Child maltreatment represents a pathogenic relational environment that confers significant risk for maladaptation across both psychological and biological domains of development. Importantly, the deleterious sequelae accompanying child maltreatment not only result in adverse consequences during childhood, but also often initiate a negative developmental cascade that continues throughout the life course (Cicchetti & Tucker, 1994; Font & Berger, 2015; Masten & Cicchetti, 2010). The proximal environment involving the nuclear family, as well as more distal factors associated with the community and culture more broadly, transact to undermine normal biological and psychological developmental processes in children who have experienced maltreatment (Cicchetti & Toth, 2006). Childhood maltreatment has been associated with increased internalizing and externalizing problems, suggesting that etiological pathways exist between these symptoms and a number of psychiatric disorders (Keyes et al., 2012). In a recent meta-analytic examination of 16 epidemiological studies with over 23,000 participants, childhood maltreatment was associated with an elevated risk of experiencing recurrent and persistent depressive episodes (Nanni, Uher, & Danese, 2012). A further meta-analysis of 10 clinical trials with over 3,000 participants found that childhood maltreatment was also related to lack of response to treatment or lack of remission of depression during treatment (Nanni et al., 2012).

The public health implications of the adverse effects accompanying child maltreatment are enormous. According to the Center for Disease Control (Fang et al., 2012), one year of confirmed cases of child maltreatment (including cases of physical, sexual, and verbal *abuse and neglect*) costs $124 billion over the lifetime of the abused children. Information garnered from the Adverse Childhood Experiences Survey (ACES; Anda, 2006), one of the largest and arguably most important public health studies in the United States, indicates that childhood trauma, including maltreatment, is associated with an extraordinary number of adult health risk behaviors, including psychosocial and substance abuse problems. Importantly, individuals with elevated ACES are also at increased risk for diseases, including diabetes, immunological and cardiovascular problems, and early morbidity. Perhaps most strikingly, the ACES findings demonstrate that childhood trauma in not a rare occurrence, with over 2/3 of the adults surveyed in this middle-income population having experienced one or more types of adverse childhood experiences and with 87% having experienced two or more types of trauma. Thus, the magnitude of the effects of childhood maltreatment and the toll it exerts on society cannot be underestimated.

Currie and Widom (2010) conducted a long-term follow-up of the effects of child abuse and neglect on economic outcomes in adulthood. They discovered that adults with documented histories of childhood abuse and/or neglect had lower levels of education, employment, earnings, and fewer assets as adults, compared with matched nonmaltreated comparisons. Currie and Widom (2010) found that there was a 14% gap between individuals with histories of abuse/neglect and nonmaltreated comparisons in the probability of employment in middle age, controlling for background demographic characteristics. Thus, abused and neglected individuals experience large and enduring economic consequences.

The sophistication of research conducted on child maltreatment has increased substantially in more recent years. Although early studies were fraught with methodological limitations, current approaches are empirically rigorous and both intervention and social policy initiatives are increasingly informed by the results of empirical studies (Toth & Cicchetti, 2006). We begin our discussion of the consequences of child maltreatment by addressing aspects related to the definition of child abuse and neglect, a fundamental issue that must be addressed if this area of research and practice is to continue to move forward.

DEFINITIONAL CONSIDERATIONS

Perhaps one of the most important advances in understanding child maltreatment was related to refining the approach to defining child maltreatment. To be able to compare findings across laboratories and effectively communicate research results more broadly to both clinicians and policymakers, systematized definitions of maltreatment are essential. Historically, consensus on an operational definition of maltreatment was lacking. Issues that contributed to difficulties in defining maltreatment included: divergence regarding what constitutes acceptable versus inappropriate parenting, uncertainty about whether to define maltreatment based on caregiver actions, child outcome, or a combination of the two, controversy over whether criteria of harm or endangerment should be utilized, and disagreements about whether similar definitions were applicable for scientific, legal, and clinical purposes.

One of the most comprehensive and sustained efforts to understand the magnitude of the problem of child abuse and neglect in the United States emanated from the National Incidence Study (NIS), a congressionally mandated effort initiated in 1974 in response to the requirements of the Child Abuse Prevention and Treatment Act.

Initially, data were collected beginning in 1979. The NIS includes not only children reported to Child Protective Services (CPS), but also those who were screened out by CPS without an investigation. Thus, NIS estimates are based on a nationally representative sample that includes both maltreated children designated as such by CPS and those identified by the community who were not officially designated as maltreated.

NIS-4, the most recent survey, was conducted in 2005 and 2006 (Sedlak et al., 2010). According to NIS classifications, maltreatment includes both abuse (physical, sexual, and emotional) and neglect (physical, emotional, educational). Standardized NIS definitions describe both acts of commission and omission for each subtype. In addition, a number of additional features such as the child's relationship to the perpetrator, the severity of the harm, and the amount of evidence existing about the perpetrator are recorded. NIS definitional standards include the Harm Standard, which is the more stringent definition requiring demonstrable harm to the child, and the Endangerment Standard, which includes children who are endangered but not yet harmed. NIS-4 reports an overall decrease in the incidence of maltreatment since NIS-3, with a 19% decrease according to the Harm Standard. When accounting for the growth in the child population during this time period, this equated to a 26% decline in maltreatment. Statistically reliable changes were not apparent in the incidence of children who experienced maltreatment according to the Endangerment Standard. Importantly, NIS-4 documents that maltreatment is also associated with a number of co-occurring risk factors, including parental unemployment, low socioeconomic status, and race. With respect to race, a higher incidence of maltreatment was observed for Black children. Because socioeconomic status and race are often highly correlated, it is difficult to disentangle the relative contributions that each of these factors may make to the increased rate of maltreatment. NIS-4 was the first U.S. survey to detect racial differences in rates of maltreatment (we will discuss this later in the chapter).

It is important to note that maltreatment is a global problem. In 2000, the National Society for the Prevention of Cruelty to Children (NSPCC) published groundbreaking information on the prevalence and impact of child maltreatment in the United Kingdom. A more recent report by NSPCC that included a random probability sample of parents, children, and young adults found similar rates of neglect but found that rates of severe child maltreatment were lower in 2009 than in 1998, suggesting a similar decline in the prevalence of maltreatment as was found in the United States (Radford, Corral, Fisher, Bassett, Howat, & Collishaw, 2011). Despite this decline, a substantial number of children continued to experience severe maltreatment, with 5.9% of children under 11 years and 18.6% of those aged 11–17 years experiencing severe maltreatment. All forms of abuse during childhood were associated with worse mental health outcomes and elevated delinquent behavior. According to NSPCC, maltreatment is defined as "all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power" (Butchart, Putney, Furniss, & Kahane, 2006, p. 9). Determination of the incidence of maltreatment is intertwined with reporting procedures and definitions utilized and, thus, the extent of documented maltreatment varies considerably across Europe and is also related to societal norms and values (Daro, 2006). Compared with incidence rates reported in the NSPCC survey, a World Health Organization prevalence study of maltreatment in Romanian families found that 24% of adolescents aged 13–14 years had experienced physical abuse, 9% had experienced sexual abuse, and 46% had experienced physical neglect (Browne, 2002). In general, between 7% and 36% of women and 3% and 29% of men internationally have experienced sexual abuse, with rates remaining constant for almost 2 decades (Finkelhor, 1994; Pereda, Guilera, Forns, & Gomez-Benito, 2009).

Despite increased agreement regarding the classification of maltreatment subtypes (Manly, 2005), some divergence remains in the field regarding how best to ascertain the presence of maltreatment. Although some advocate for reliance on information obtained from officially documented reports of maltreatment (Manly, 2005), other investigators maintain that caregiver and child reports are preferable because inclusion only of officially documented cases may result in only the most severe forms of maltreatment being captured. Moreover, more recently child protective systems have begun utilizing less adversarial approaches to families who have engaged in less severe forms of maltreatment. Therefore, cases that may have been indicated as veridical maltreatment a decade ago no longer appear as such on official roles. Ideally, a multipronged approach to defining maltreatment is preferable, including systematic coding of documented reports, access to information obtained in medical records, and interview information from caregivers and children. One system for coding official records examined in the aforementioned study, the MCS (Barnett et al., 1993) captures not only

subtype of maltreatment but also dimensions such as severity, frequency/chronicity, perpetrators, and developmental periods during which maltreatment occurred. The MCS has been used in more than 50 research laboratories in both the United States and Europe and has demonstrated excellent reliability and validity. To obtain supplementary information, the Maternal Maltreatment Classification Interview (MMCI; Cicchetti, Toth, & Manly, 2003) also can be administered to caregivers. Other widely utilized measures for assessing childhood maltreatment include the Childhood Experience of Care & Abuse instrument (Bifulco, Brown, & Harris, 1994) and the Childhood Trauma Questionnaire (Bernstein & Fink, 1998).

Despite advances related to improved definitions of child maltreatment, far too many investigations fail to utilize validated classification systems or to provide comprehensive information on the maltreatment experience. Issues related to the perpetrator of maltreatment, chronicity and severity of maltreatment, and when in the developmental period maltreatment occurred frequently are not considered. Attainment of a comprehensive portrayal of maltreatment becomes even more difficult in retrospective investigations that rely on the recall of maltreated individuals. Moreover, societal mores and attitudes toward corporal punishment vary considerably across cultures and further complicate estimates on the incidence and prevalence of child maltreatment. Issues such as these continue to contribute to discrepant conclusions across investigations and warrant increased attention in future studies (Baker, 2009; Barnett et al., 1993).

In addition to arriving at a consensus on how child maltreatment is defined, considerations regarding conceptualization of the etiology of child maltreatment are of paramount importance in investigations of maltreatment.

ETIOLOGICAL MODELS OF CHILD MALTREATMENT

In discussing the etiology of child maltreatment, it is important to recognize that most forms of maltreatment are part of a pattern of maladaptive behavior that emerges over time. Early views on the development of maltreatment emerged from a main effects perspective, in which it was thought that single risk factors such as parental psychopathology, poverty, or a parental history of maltreatment could provide an etiological account of the occurrence of child maltreatment (Cicchetti & Rizley, 1981). These unidimensional views on the etiology of child maltreatment soon gave way to more complex causal models, as it became clear that no single risk factor or set of risk factors would explain the development of maltreatment (Belsky, 1980; Cicchetti & Rizley, 1981).

Applying Bronfenbrenner's (1979) theory of human development, the etiological model proposed by Belsky (1980) initiated dramatic changes in the conceptualization of child maltreatment, as it necessitated the consideration of the broader environment in which maltreatment occurs. According to Belsky, child maltreatment is a social-psychological phenomenon that cannot be understood in isolation from the community and the culture within which the family and the individual are embedded. As such, his model contains four levels of analysis: the *macrosystem*, including the cultural beliefs and values that contribute to and influence child maltreatment; the *exosystem*, including aspects of the community that contribute to the incidence of maltreatment; the *microsystem*, including factors within the family that contribute to the occurrence of maltreatment; and *ontogenetic* development, including factors within the individual that are associated with being a perpetrator of maltreatment. Given that proximity to the individual increases with each subsequent level of the ecology (from the macrosystem to the ontogenetic context), Belsky further highlighted that risk factors at ecological levels that are closer to the individual exert a more direct influence on an individual's development. Moreover, interactions exist between and among all levels of the ecology, contributing to and influencing the occurrence of child maltreatment.

Cicchetti and Rizley (1981), drawing on the work of Sameroff and Chandler (1975), introduced additional elements to the etiological model of maltreatment by proposing a transactional model. This model focused on the reciprocal interactions of the environment, the caregiver, and the child, which together contribute to the outcomes of child development. An important distinction was made between two classes of risk factors: those that are potentiating, thereby increasing the risk for maltreatment, and those that are compensatory, which decrease the risk for maltreatment. Additionally, a temporal dimension was added to distinguish between risk factors that are transient versus those that are enduring. By combining these categorical and temporal dimensions of risk factors, Cicchetti and Rizley (1981) proposed four classes of determinants for the occurrence of child maltreatment:

1. *Enduring vulnerability factors* include all relatively long-lasting factors, conditions, or attributes that serve to potentiate maltreatment. These may involve parental, child, or environmental characteristics. Vulnerability

factors may be biological in nature, historical (e.g., a parent with a history of being maltreated), psychological, and sociological.

2. *Transient challengers* include short-term conditions and stresses such as loss (of status, a job, or a loved one), physical injury or illness, legal difficulties, marital or family problems, discipline problems with children, and the emergence of a child into a new and more difficult developmental period.
3. *Enduring protective factors* include relatively permanent conditions that decrease the risk of maltreatment. Examples of likely protective factors include a parent's history of good parenting and a secure quality of intimate relationship between the parent figures.
4. *Transient buffers* include factors that may protect a family from stress, such as sudden improvement in financial conditions, periods of martial harmony, and a child's transition out of a difficult developmental period.

It is the transactions among ecological levels that result in potentiating and compensatory factors and in mechanisms for the precursors and sequelae of child maltreatment. The Cicchetti and Rizley (1981) model conceptualized the risk for child maltreatment as probabilistic, proposing that the likelihood of maltreatment occurring is determined by the balance among risk and protective factors and processes. Overall, the balance of potentiating and compensatory factors that are present in the various ecological levels is thought to determine in a probabilistic fashion the absence or presence of child maltreatment.

Integrating the etiological models of Belsky (1980) and of Cicchetti and Rizley (1981), Cicchetti and Lynch (1993) proposed the ecological-transactional model of child maltreatment. By incorporating the ideas of the average expectable environment (Cicchetti & Lynch, 1995) and probabilistic epigenesis (Gottlieb, 1992) into a broad integrative framework, this model explains how processes at each level of the ecology exert reciprocal influences on each other and shape the course of child development (Cicchetti & Lynch, 1993). As such, potentiating and compensatory risk factors associated with maltreatment are present at each level of the ecology and can influence processes in the surrounding environmental levels. These dynamic transactions, which operate both horizontally and vertically throughout the levels of ecology, determine the amount of risk for maltreatment that an individual faces at any given time. The levels of ecology most proximal to the child have the most direct impact on child development relative to the more distally located macrosystem (Cecil, Viding, Barker, Guiney, & McCrory, 2014; Lynch & Cicchetti, 1998a; Maughn & Cicchetti, 2002). Although characterized by an overall pattern in which risk factors outweigh protective factors, there are infinite permutations of these risk variables across and within each level of the ecology, providing multiple pathways (known as equifinality) to the occurrence of maltreatment.

It is important to consider that factors that increase or decrease the likelihood of risk during one period of children's development may not do so during other developmental periods. Moreover, the temporal dimension of potentiating and compensatory risk factors is not static. Risk factors that are enduring can become transient and vice versa. For example, potentiators that originally are associated with relatively transient factors, such as initial unemployment, can become enduring when they persist over time, as in the case of chronic unemployment. Risk factors that had acted as potentiators can also be associated later on with compensatory risk factors. Perhaps the successful handling of a challenge can result in the development of new compensatory factors. For example, children who are able to survive the direct and indirect challenges presented by such potentiating factors as child maltreatment, poverty, and community violence develop inner characteristics that later are able to function as compensatory factors. The reverse is also possible. A compensatory risk factor could become a potentiating risk factor for maladaptation. Behaviors that are positive at one developmental period, such as a young child's dependence on a caregiver for support, might become counterproductive if continued into late adolescence, when more autonomy is expected.

Ultimately, it is the child's own ontogenetic processes, as manifested by the particular developmental pathway that individuals engage that culminate in eventual adaptation or maladaptation. The challenges or supports presented to children by the family, community, and society contribute to these ontogenetic processes; however, children also play an active role in their organismic development as they respond to these influences and engage in the resolution of stage-salient developmental issues. In the case of child maltreatment, one could imagine how the increased presence of enduring vulnerability factors and transient challenges associated with maltreatment at each level of ecology contributes to unsuccessful resolution of stage-salient developmental issues, setting the child on a pathway to maladaptive developmental outcomes and psychopathology (Cicchetti & Toth, 2006). The ecological-transactional model of Cicchetti and Lynch (1993) may also aid in providing an account for resilient outcomes. The presence of enduring protective factors may approximate features

of the average expectable environment, thus allowing some children to display successful adaptation in the face of maltreatment (Cicchetti, 2013).

We next turn our attention toward the effects of child maltreatment, with a particular focus on the developmental processes involved.

SEQUELAE OF CHILD MALTREATMENT

Empirical research on the developmental sequelae of child maltreatment has been conducted for the past half century. Studies of the consequences of maltreatment are very important for enhancing the quality of clinical, legal, and policy-making decisions for maltreated children. Decisions concerning such issues as whether to report a child as maltreated, whether to remove a child from the home, how to develop interventions to meet the specific psychological needs of maltreated children, and how to evaluate the efficacy and the effectiveness of these interventions all necessitate a solid and sophisticated data base on the developmental sequelae of child maltreatment. As Aber and Cicchetti (1984) cautioned, "Without rigor in design and method . . . myth will be put forward in place of knowledge as a guide to social action" (pp. 196–197).

Child abuse and neglect represent a severe dysfunction in parenting, as well as a substantial disturbance in parent–child relationships that may result in serious child maladaptation and aberrant development across the life span (Belsky & Jaffee, 2006). In fact, child maltreatment may constitute the greatest failure of the caregiving environment to provide opportunities for normal development (Cicchetti & Lynch, 1995). Moreover, maltreatment experiences may provide serious challenges to the species-typical organism-environment coactions that play important roles in the emergence and timing of normal developmental change.

The most important early study of the developmental consequences of child abuse and neglect is also the most controversial. Previously, none of the studies investigating the effects of child abuse and neglect had employed a matched comparison group; however, Elizabeth Elmer (1977) studied abused children matched on age, race, gender, and socioeconomic status (SES) to a group of children who had experienced accidents but were not abused. The abused children and the accident children initially were studied when they were approximately 12 months of age. These children were followed up again eight years later. Additionally, Elmer added a nontrauma comparison group of children at the follow-up assessment.

The major findings of the study were the absence of group differences in health history, intellectual status in school, language development, and self-concept. Despite the maltreatment classification, measurement, conceptual, and sampling flaws in the study (see Aber & Cicchetti, 1984), Elmer concluded that membership in the low-SES may have as profound an impact as abuse on child development. Elmer's conclusion placed the issue of what constitutes developmental risk in a stark sociopolitical light. It was essential that future investigations transcend the scientific flaws of Elmer's study (see Aber & Cicchetti, 1984).

Developmental scientists took up the challenge during the 1980s and began conducting investigations of the sequelae of child maltreatment (see, e.g., Cicchetti & Carlson, 1989; Egeland & Sroufe, 1981; Lamb, Gaensbauer, Malkin, & Schultz, 1985). Consistent with the tenets of the field of developmental psychopathology, these investigators believed that it was possible to learn more about an individual's normal functioning by studying its pathology and, likewise, more about its pathology by studying its normal conditions (Cicchetti, 1984; Cicchetti & Toth, 2009; Sroufe & Rutter, 1984). It was thought that theorizing about development without considering deviations that might be expected from the prominent and wide-ranging intra- and extraorganismic disturbances, as well as the transactions that occur among them, would eventuate in incomplete and ambiguous accounts of developmental processes. Methodologically rigorous examinations of the consequences of child maltreatment, in comparison to comparable groups of nonmaltreated children drawn from low-SES environments and informed by developmental theory and research, provided researchers with an excellent opportunity to test the veridicality of Elmer's (1977) conclusions and to uncover potential developmental deviations, as well as the ecological disturbances associated with them. These initial developmentally informed and well-designed investigations, as well as decades of subsequent sound research, unquestionably demonstrate that the deleterious effects of child maltreatment transcend those of poverty (Cicchetti & Toth, 2005).

The study of maltreated children can make numerous contributions to the processes underlying normal development—primarily through contributing precision to developmental theory, affirming it, challenging it, and impelling theoreticians and researchers to examine extant developmental theories more critically in relation to knowledge about maladaptation, psychopathology, and resilience. Conversely, before one is capable of grasping deviances that exist in a developing system, one must

also possess an accurate description of the system itself. To comprehend how abnormalities are transmitted from one developmental level to another, we must know how the normal transitions from one level of functioning to another are accomplished. Only when we understand the total ongoing development of normal systems can we comprehend developmental deviations as adaptational irregularities of those systems (Cicchetti, 1984, 1993; Sameroff, 1983; von Bertalanffy, 1968).

Through investigations of the effects of severe environmental disturbances such as child abuse and neglect, researchers may be able to gain insight into processes that normally are so subtle and gradual that they are not observed. For example, by examining the development of children who have not experienced a benign rearing environment, such as is the case with children who have been maltreated, researchers may be able to elucidate the impact that the quality of caregiving can exert on neurobiological structure and function (Belsky & deHaan, 2011; Cicchetti, 2002a, 2002b).

Research on child maltreatment also informs, and can be informed by, the significant functions of normal parenting (Belsky & Vondra, 1989; Rogosch, Cicchetti, Shields, & Toth, 1995). The specific acts of omission and commission that define child maltreatment are salient features of maltreated children's microsystems. It is in this immediate context of deviant parenting that maltreated children's atypical development takes shape. Close analysis of the maltreating caregiving environment and its links with poor developmental outcomes can shed light on the protective processes associated with appropriate parenting.

Investigations of the determinants of resilient functioning in maltreated children also can provide information about the multiple possible pathways of development. Despite having different specific experiences, many maltreated children exhibit similar failures in the stage-salient tasks of development (i.e., equifinality). On the other hand, not all maltreated children are equally affected by their experiences (i.e., multifinality) with some achieving resilient outcomes and the rest exhibiting maladaptive development (Cicchetti, 2013). Research investigations of maltreated children's development and struggles with adaptation can teach us about the range and variability of individual response to challenge and adversity. Instances of maltreated children succeeding at particular developmental tasks or who otherwise achieve resilient adaptation can teach us about the self-righting properties inherent to development despite poor quality care (Sameroff & Chandler, 1975; Waddington, 1957). On the other hand, findings that reveal the relative rarity with which maltreated children display resilient outcomes highlight some of the real constraints on children's self-righting abilities.

Although a comprehensive review of the sequelae of child maltreatment is not addressed in the present chapter, we cover developmental issues that forebode later maladaptation in the absence of efficacious evidence-based intervention. Moreover, although some investigations reveal negative sequelae associated with specific subtypes of maltreatment, it is extremely difficult to disentangle specific effects of maltreatment by subtype given their frequent overlapping occurrence. As investigations continue to refine definitions of dimensions of maltreatment, it will be increasingly possible to ascertain if there are any sequelae that are more likely to be associated with a specific subtype of maltreatment.

THE ORGANIZATIONAL PERSPECTIVE ON DEVELOPMENT

Much research conducted on the effects of child abuse and neglect is guided by the ecological-transactional model and an organizational perspective on development, a powerful theoretical framework for conceptualizing the intricacies of a life span approach to risk and resilience, as well as to normal development (Cicchetti, 1989; Cicchetti & Toth, 1995, 1998; Sroufe, 1997; Sroufe & Rutter, 1984). The organizational perspective focuses on the quality of integration both within and between the biological and psychological systems of the individual. Moreover, the organizational perspective addresses how development occurs, specifically identifying a progression of qualitative reorganizations within and among the biological and psychological systems that proceed through differentiation and subsequent hierarchical integration (Werner & Kaplan, 1963). In accord with the organizational perspective, development is not viewed as consisting of a series of tasks that need to be accomplished and that subsequently decrease in importance. Rather, development is conceived as comprising a number of age- and stage-relevant tasks. Although the salience of these tasks may wane in relation to newly emerging issues, the tasks remain important to adaptation over time (Cicchetti, 1993). A hierarchical picture of adaptation emerges in which the successful resolution of an early stage-salient issue increases the probability of subsequent successful adjustment (Sroufe & Rutter, 1984). As each new stage-salient issue comes to the fore, opportunities for growth and consolidation, as well as challenges associated with new vulnerabilities, arise. These tasks include the development of emotion regulation, the

formation of attachment relationships, the development of an autonomous self, the formation of effective peer relationships, and successful adaptation to school. To our knowledge, little research has been conducted on the stage-salient issues of adolescence and emerging adulthood in child maltreatment, such as psychological autonomy, forming close relationships within and across gender, and deriving a cohesive sense of self-identity (Cicchetti & Rogosch, 2002; Masten & Coatsworth, 1998). These issues deserve future research attention.

Despite the fact that more distal historical factors and current influences are important to the process of development, individual choice and self-organization have increasingly been viewed as exerting critical influences on development (Cicchetti & Rogosch, 1997; Cicchetti & Tucker, 1994). Across the developmental course, the evolving capacities of individuals and their active choices allow for new aspects of experience, both internal (e.g., genetic/biological) and external, to be coordinated in increasingly complex ways. Moreover, not only because biological factors can influence psychological processes, but also because social and psychological experiences exert actions on the brain by feeding back on it to modify gene expression and brain structure, function, and organization (Cicchetti & Tucker, 1994; Eisenberg, 1995; E. R. Kandel, 1998; Szyf & Bick, 2013), developmental plasticity can be brought about by both biological and psychological self-organization (Cicchetti, 2002a; Cicchetti & Tucker, 1994). Thus, for example, the fact that most maltreated children evidence at least some self-righting tendencies in the face of extreme adversity attests to the strong biological and psychological strivings toward resilience that virtually all humans and living organisms possess (Cicchetti & Curtis, 2006; Cicchetti & Rogosch, 1997; Waddington, 1957). In contrast, the absence of such resilient self-strivings in some maltreated children attests to the deleterious and pernicious impact that traumatic experiences can exert on core biological and psychological developmental processes. We next address the effects of maltreatment on stage-salient issues.

AFFECT DIFFERENTIATION AND EMOTION REGULATION

An early stage-salient issue in infancy involves the ability to differentiate and regulate emotions. Conceptualized as the monitoring, evaluating, and modifying of emotional reactions for the purpose of achieving individual goals, emotion regulation optimizes one's adaptive engagement with the environment (Thompson, Lewis, & Calkins, 2008). Cicchetti, Ackerman, and Izard (1995) argued that emotion regulation is critical both in initiating, motivating, and organizing adaptive behavior, and in preventing stressful levels of negative emotions and maladaptive behavior.

Emotion regulation is a developmentally acquired process that emerges from increasing differentiation and hierarchical integration of biological and psychological systems. Emotion regulation evolves as a function of both intrinsic features and extrinsic socio-emotional experiences within the context of early parent–child interactions (Cicchetti, Ganiban, & Barnett, 1991). At the biological level, important intra-organismic factors for the development of emotion regulation include individual differences in genotypic variation, organizational changes in central nervous system structure and function, cerebral hemispheric lateralization, and the development of neurotransmitter systems. Extra-organismically, children's emotional experiences, expressiveness, and arousal are influenced by caregivers' response to and tolerance of affect (Sroufe, 1996). Parents' socialization of affect displays during early interpersonal exchanges serves as the model through which aspects of emotional regulation may be learned (Hesse & Cicchetti, 1982; Thompson et al., 2008).

Child maltreatment represents a significant threat to the optimal development of affective processing abilities. Given the severe disturbances in the average expectable environment provided by maltreating families, considerable evidence has mounted to demonstrate the detrimental effects of aspects of maltreatment on children's emotional development and regulation. Specifically, maltreated children have shown deviations in emotion expression, recognition, communications, and understanding (Cicchetti & Ng, 2014). Moreover, in accord with the organizational perspective, adequate emotion regulation serves as a foundation for the development of secure attachment relationships, an autonomous and coherent self-system, and effective relationships with peers, whereas early affect-regulatory failures increase the probability that a child will develop future insecure disorganized attachment relationships, self-system impairments, and peer difficulties (Cicchetti & Valentino, 2006).

Divergence in maltreated children's emotional expression has been noted as early as 3 months of age, where severely physically abused infants have evinced increased rates of fearfulness, anger, and sadness during mother-infant interactions (Gaensbauer, Mrazek, & Harmon, 1981). The expression of fear and anger among physically abused infants at 3 months of age is a

particularly salient finding considering that the normative ontogenetic development of these affects does not typically occur until approximately 7 to 9 months of age (Sroufe, 1996). In contrast, neglected infants have been shown to display an attenuated range of emotional expression and an increased duration of negative affect as compared with nonmaltreated infants (Gaensbauer et al., 1981). Thus, excessive amounts of negative affect or blunted patterns of affect have been observed in maltreated infants long before they occur in normal development.

It is likely that early malevolent care accelerates the development of negative affect circuitry in the brains of maltreated infants. This may be accomplished by excessive synaptic pruning of the positive affect neurobiological circuits as a result of inadequate or insufficient early positive experiences by abused babies. The accelerated development of negative affect circuitry may lay the groundwork for the negativity bias (Ayoub et al., 2006) manifested by abused children in behavioral and psychophysiological studies of attention to facial expressions and in studies of social information processing (Pollak, 2005; Teisl & Cicchetti, 2008). Thus, maltreated children may already be at risk for developing differential emotion regulation developmental pathways by 3 months of life.

The early maladaptive processing of stimuli that contributes to affective regulatory problems may lay the foundation for future difficulties in modulating affect. Corroboration for the prediction, emanating from the organizational perspective, that maltreated children are at increased risk for evidencing a developmental progression from affect-regulatory problems to behavioral dysregulation, has been obtained in a number of cross sectional investigations. Maltreated toddlers have been shown to react to peer distress with poorly regulated and situationally inappropriate affect and behavior, including anger, fear, and aggression, as opposed to the more normatively expected response of empathy and concern (Main & George, 1985). Likewise, maltreated preschool and school-age children have been found to exhibit a range of dysregulated behaviors that are frequently characterized by disruptive and aggressive situations. In addition, physically abused preschool boys who witnessed an angry simulated interaction directed at their mothers evinced greater aggressiveness and more coping directed toward the alleviation of maternal distress than did nonabused boys (Cummings, Hennessy, Rabideau, & Cicchetti, 1994).

Shields, Cicchetti, and Ryan (1994) have shown in an observational study that maltreated children are deficient in affective and behavioral regulation, and that this attenuated self-regulation mediates the negative effects of maltreatment on children's social competence with peers. In accord with an organizational perspective, although affective and behavioral self-regulatory processes were interrelated, each appeared to represent a distinct developmental system that differentially and individually affects children's competence. Finally, in an investigation of 4- to 6-year-old children, approximately 80% of maltreated preschoolers exhibited patterns of emotion dysregulation (i.e., undercontrolled/ambivalent and overcontrolled/unresponsive types) in response to witnessing inter-adult anger, compared with only 37% of the nonmaltreated comparison children. Undercontrolled/ambivalent emotion regulation patterns were associated with maternal reports of child behavior problems and were found to mediate the link between maltreatment and children's symptoms of anxiety or depression (Maughan & Cicchetti, 2002). Findings such as these support a sensitization model whereby repeated exposure to anger and familial violence results in greater emotional reactivity.

During the school-age years, children continue to develop emotion regulation skills as they encounter increasing socialization demands from peers as well as from family. In an investigation conducted in the context of a research summer day camp, Shields and Cicchetti (1998) examined the interplay among emotion, attention, and aggression in a sample of school-age maltreated and nonmaltreated children. A central focus of this investigation was to examine mechanisms underlying maltreatment's deleterious effects on behavioral and emotional dysregulation.

Shields and Cicchetti (1998) found that maltreated children were more verbally and physically assaultive than were the nonmaltreated comparison children, with physical abuse placing children at heightened risk for aggression. Maltreated children also were more likely than comparison children to exhibit the distractibility, overactivity, and poor concentration characteristic of children who experience deficits in attention modulation. Physically and sexually abused children also displayed attention disturbances suggestive of subclinical or nonpathological dissociation, including daydreaming, blank stares, and confusion. Deficits in emotion regulation also were evident, in that maltreated children were less likely than comparison children to show adaptive regulation and more likely to display emotional lability/negativity and contextually inappropriate emotion expressions. Such pervasive deficits in maltreated children's regulatory capacities are cause for special concern, as the ability to modulate behavior, attention, and emotion underlie children's adaptive functioning in a number of key domains, including self-development,

academic achievement, and interpersonal relationships (Cicchetti, 1989, 1991; Shonk & Cicchetti, 2001).

Shields and Cicchetti (1998) also demonstrated that impaired capacities for attention modulation contribute to emotion dysregulation in maltreated children. Specifically, attention deficits mediated maltreatment's effects on emotional lability/negativity, inappropriate affect, and attenuated emotion regulation. Attention processes that suggest subclinical or nonpathological dissociation also contributed to maltreated children's deficits in emotion regulation. Thus, abuse seems to potentiate disruptions in attention that result in both a relative detachment from and unawareness of one's surroundings, as well as in hyperattunement and hyperreactivity to the social surround (Pollak & Tolley-Schell, 2003; Rieder & Cicchetti, 1989). Together, these deficits appear to compromise maltreated children's ability to regulate behavior and affect in social settings.

In another investigation, Shields and Cicchetti (2001) examined children who were maltreated by their caregivers to ascertain whether these children would be more likely to bully others and to be at increased risk for victimization by peers than would nonmaltreated comparison children. An additional focus was to investigate emotion's role in bullying and victimization among maltreated children. Maltreated children were found to be more likely than nonmaltreated children to bully other children. Bullying was especially prevalent among abused children who experienced maltreating acts of commission (physical or sexual abuse). Maltreatment also placed children at risk for victimization by peers. As expected, both bullies and victims evidenced problems with emotion regulation. Furthermore, logistic regression analyses suggested that emotion dysregulation made a unique contribution to differentiating bullies and victims from children who did not evince bully or victim problems. Additionally, maltreatment's effects on children's risks for bullying and victimization were mediated by emotion dysregulation.

In a short-term longitudinal study, Kim and Cicchetti (2010) found that children who are more adept at regulating negative emotions show higher social competence in peer interactions and higher peer competence, resulting in lower levels of internalizing symptomatology. In contrast, poor emotion regulation is a significant predictor of both maladaptive social functioning, such as peer rejection and internalizing symptomatology. Furthermore, Kim-Spoon, Cicchetti, and Rogosch (2013) investigated the longitudinal contributions of emotion regulation and emotion lability-negativity to internalizing symptomatology. A sample of over three hundred maltreated ($N = 171$) and nonmaltreated ($N = 151$) children were followed from age 7 to 10 years. For both maltreated and nonmaltreated children, emotion regulation was a mediator between emotion lability-negativity and internalizing symptomatology, whereas emotion lability-negativity did not mediate the relation between emotion regulation and externalizing symptomatology. Early maltreatment was associated with high emotional lability-negativity (age 7) that contributed to poor emotion regulation (age 8), which in turn was predictive of increases in internalizing symptomatology (from age 8 to 9).

These findings suggest that emotion regulation and emotion lability-negativity may be important factors in identifying distinct pathways to child psychopathology. Specifically, low emotion lability-negativity and adaptive emotion regulation appear to play protective roles in the development of internalizing symptomatology. The findings also suggest that emotion regulation is an important mediational process between emotion lability-negativity and internalizing symptomatology. Therefore, to alter emotional processes that are related to the subsequent development of internalizing symptomatology, a focus on improving emotion regulation skills in children is likely to be an effective strategy that can impede the progression of internalizing problems. The results also imply that emotion regulation can be targeted to reduce the deleterious effects of emotion lability-negativity heightened by early maltreatment experiences, thus preventing internalizing symptomatology.

In a particularly important mega-analytic study designed to examine the effects of family violence on children's behavioral problems, Sternberg and colleagues found that children who experienced multiple forms of family violence were at heightened risk for behavior problems compared with those who experienced only a single type of violence (Sternberg, Baradaran, Abbott, Lamb, & Guterman, 2006). Regardless of type of abuse, age, or gender, more children had behavior problems in the nonclinical than in the clinical range. This was the case even for children who were abused and also witnessed family violence, where only 28–50% of the children in any group had clinically significant behavior problems. These results highlight the remarkable resilience that can be present, even in the context of extreme family adversity.

EMOTION RECOGNITION

To examine the affective input that maltreated children receive, Camras and colleagues (1988, 1990) conducted a series of investigations of maternal facial expressions. When asked to deliberately produce facial expressions, maltreating mothers' demonstrations of emotion faces were

less easily identified by observers than were the expression of nonmaltreating mothers (Camras et al., 1988). During mother-child interactions, maltreating mothers differed from nonmaltreating mothers with regard to the expression of sadness (Camras et al., 1990). Taken together, the emotion displays of abused and neglected infants highlights the centrality of interactions with caregivers in shaping the development of affect expression or differentiation. Moreover, maternal emotional expression ability contributes to their children's ability to recognize facial emotions (Camras et al., 1988).

Difficulties in mentally representing and processing social information have also been noted in children with histories of maltreatment. Children who have been neglected have difficulty discriminating emotional expressions, whereas physically abused children demonstrate a response bias to angry emotional expressions (Pollak, Cicchetti, Horning, & Reed, 2000). Pollak et al. (2000) hypothesized that physically abused preschool children would demonstrate an increased sensitivity to anger-related cues, perhaps also resulting in decreased attention to other emotional cues. The results of their study revealed that, when physically abused children were exposed to a perceptual scaling task, they perceived angry faces as highly salient and more distinctive than other emotion categories (Pollak et al., 2000). Additionally, when asked to match facial expressions to an emotional situation, physically abused children showed a response bias for anger such that, when they were uncertain which facial expression to choose, they showed a lower threshold for selecting anger. Pollak and Sinha (2002) further demonstrated that physically abused children required less sensory input than did comparison children to accurately identify facial displays of anger. Pollak and Sinha utilized a gradual evolution of images depicting facial expressions of various emotions. Physically abused children detected angry emotions at lower steps of the sequence but did not exhibit increased sensitivity for the other facial displays. The authors concluded that physically abused children have facilitated access to representations of anger. Similarly, in a task in which pairs of photographs of emotional expressions were morphed into each other (Pollak & Kistler 2002), physically abused children detected anger with lower signal strength than did controls. In combination, these studies suggest that physically abused children can detect facial expressions of anger more accurately and at lower levels of perceptual intensity than other emotions.

In an investigation of the attentional mechanism underlying the finding that physically abused children overattend to angry experiences, Pollak and Tolley-Schell (2003) found that children who had experienced physical abuse demonstrated delayed disengagement when angry faces served as invalid cues and exhibited increased attention to valid angry trials. These results suggest that early adverse experiences influence maltreated children's selective attention to threat-related signals.

In addition, Pollak, Vardi, Bechner, and Curtin (2005) examined the effects of early child physical abuse on 4-year-old children's regulation of attention in the presence of interpersonal hostility. Pollak et al. (2005) measured abused children's reactions to the unfolding of a realistic interpersonal emotional situation through multiple methods, including autonomic nervous system changes (i.e., heart rate; skin conductance level) and overt behavioral performance on an attention task. Although the physically abused and nonabused comparison children did not differ in terms of their baseline levels of arousal, marked differences emerged in physically abused children's regulatory responses to background anger. The findings suggest that children with physical abuse histories exhibit anticipatory monitoring of the environment in response to the emergence of anger. Relatedly, Pollak, Messner, Kistler, and Cohn (2009) presented abused children with arrays of stimuli that depicted the unfolding of facial expressions, from neutrality to peak emotions. These investigators found that abused children were able to recognize anger early in the formation of the facial expression, when few physiological cues were available. The speed of children's recognition was associated with the degree of self-reported anger/hostility by the child's parent. Thus, these findings highlight the ways in which perceptual learning can shape the timing of emotion perception.

Perlman, Kalish, and Pollak (2008) conducted an investigation of emotion understanding in maltreated and nonmaltreated children. To assess how well children understood the antecedents of emotional reactions in others, children were presented with a variety of emotional situations that varied in outcome and equivocality. Children were told the emotional outcomes and asked to rate whether a situation was a likely cause of such an outcome. The investigators tested the effects of maltreatment experience on children's ability to map emotion to their eliciting events and their understanding of emotion-situation pairings. Nonmaltreated children were able to distinguish between common elicitors of positive and negative events, whereas children who developed within maltreating contexts interpreted positive, negative, and equivocal events as being equally plausible causes of sadness and anger.

Maltreated children are exposed to an atypical emotional environment, characterized by less positive emotion (Bugental, Blue, & Lewis, 1990) and more negative emotion (Herrenkohl, Herrenkohl, Egolf, & Wu, 1991) in

comparison to that expressed in nonmaltreating homes. Among maltreating families, physically abusive parents are more negative than neglecting parents and engage in higher rates of aggression directed toward their children. Neglected children experience an impoverished emotional environment, marked by infrequent affective exchanges with their caregivers (Crittenden, 1981). Ultimately, it is believed that these aberrant emotional experiences eventuate in neuropathological connections that undermine effective emotion-regulation capabilities.

Shackman et al. (2010) evaluated the quality of facial and vocal emotional expressions in abusive and nonabusive mothers and assessed whether mothers' emotional expression quality was related to their children's cognitive processing of emotion and behavioral problems. Relative to nonabusive mothers, abusive mothers produced less prototypical angry facial expressions, and less prototypical angry, happy, and sad vocal expressions. In addition, children's cognitive processing of their mothers' angry faces was related to the quality of mothers' facial expressions. The finding that abusive mothers' expressions of anger were characterized by less intensity and arousal may lead to their children interpreting these expressions of anger as hard to predict and more difficult to interpret (Shackman et al., 2010). Accordingly, abused children's exposure to poorer quality emotional signals may deprive them of an important source of information about the meaning of emotional expressions.

Psychophysiological studies also provide evidence that maltreated children allocate more attentional resources to the detection of anger (Pollak, Klorman, Thatcher, & Cicchetti, 2001). In particular, measurement of cognitive event-related brain potentials (ERP) indicates that school-age maltreated children display larger P3b amplitude when their attention is directed toward angry, as opposed to happy, targets (Pollak et al., 2001; Pollak & Tolley-Schell, 2003; Shackman, Shackman, & Pollak, 2007). Moreover, this pattern of response appears to be specific to anger, rather than to negative emotions in general (Pollak et al., 2001). Similar findings indicate that maltreated infants exhibit brain-based abnormalities in the processing of facial affect as early as 15 months of age (Curtis & Cicchetti, 2013). Together, these results suggest more efficient cognitive organization and processing of anger among abused children.

Behavioral and psychophysiological evidence of maltreated children's differential processing of affective information suggests that early experience influences subsequent emotional development and shapes implicated brain circuitry (Cicchetti, 2002a). The effects observed among maltreated children may reflect experience-dependent processes that involve the fine-tuning of attention, learning, perceptual, and memory systems that facilitate the rapid identification of anger (Pollak, 2009).

For the physically abused child, displays of anger may be the strongest predictor of threat; however, increased sensitivity to anger could result in decreased attention to other emotional cues. Conversely, the neglected child may suffer from an extremely limited emotional learning environment. A solution to the problem created for maltreated children by aberrant emotional signals from parents may be general constraints imposed on children in the form of immature or limited resources, which require young children to filter or select some environmental cues over others (Bjorklund, 1997). This developmentally normal aspect of selective attention suggests that, irrespective of the initial state of the organism, emotional development is contingent on the nature of the input or experiences made available to the child.

In a recent meta-analysis examining emotion recognition and understanding in children with histories of maltreatment (including abuse and/or neglect), maltreated children evidenced poorer performance on a range of indicators (Luke & Banerjee, 2013). Moderator analyses revealed more pronounced deficits in emotion understanding than in emotion recognition. Developmental effects were also found, with poorer performance emerging in early and middle childhood, but not in adolescents and adults. Taken in conjunction with the extant body of research, this meta-analysis confirms that maltreated children evidence deficits in a wide range of skills associated with social understanding. The meta-analysis also highlights the importance of future investigations utilizing a developmental framework and striving to disentangle the effects of specific dimensions of maltreatment on functioning.

FORMATION OF ATTACHMENT RELATIONSHIPS

The establishment of a secure attachment relationship between an infant and his or her caregiver represents a primary task during the first year of life. As development proceeds, attachment theorists have posited that a secure attachment relationship provides a base from which to explore and, ultimately, contribute to the integration of cognitive, affective, and behavioral capacities that influence ongoing and future relationships, as well as the understanding of the self (Bowlby, 1969; Sroufe, 1990). Children construct internal working models of

their attachment figures out of their interactions with their caregivers, their own actions, and the feedback they receive from these interactions. Once organized, these internal working models tend to operate outside of conscious awareness and are thought to be relatively resistant to change. Children formulate their conceptions of how acceptable or unacceptable they are in the eyes of their attachment figures (i.e., their self-image) based on their interactional history with their primary caregivers. Maltreated children experience distortions of the caregiving environment in which internal working models develop. Exposed to insensitive and pathological care, maltreated children develop negative expectations regarding the availability and trustworthiness of others, as well as mental representations of the self as incompetent and unworthy.

There are differences in the expression of internal working models between maltreated and nonmaltreated children (Pickreign Stronach et al., 2011; Toth, Cicchetti, Macfie, Maughan, & Vanmeenen, 2000). For example, Toth, Cicchetti, Macfie, and Emde (1997) found that maltreated children had significantly more negative maternal and self-representations. Furthermore, physically abused children had a greater number of negative representations than children who had experienced other subtypes of maltreatment.

Maltreated children are especially at risk for developing insecure disorganized attachments (see Cyr, Euser, Bakermans-Kranenburg, & van IJzendoorn, 2010 for a meta-analysis). Estimates of the manifestation of disorganized attachment among maltreated children range from 80% to over 90% (Cyr et al., 2010). In the Strange Situation paradigm, Type D infants demonstrate inconsistent and disorganized strategies for coping with separations from and reunions with their caregivers (Hesse & Main, 2006). In addition, these infants display bizarre behaviors such as freezing, stilling, and stereotypies, as well as contradictory behavior directed toward their attachment figures (e.g., approaching their parent with heads averted; Hesse & Main, 2006).

A number of explanations have been proffered to account for the preponderance of disorganized attachment relationships between maltreated children and their primary caregivers. Because inconsistent care is a hallmark of maltreating families (Rogosch et al., 1995), some have hypothesized that the combination of insensitive overstimulation and insensitive understimulation may lead to the contradictory behaviors observed among maltreated infants classified as type D. According to Hesse and Main (2006), attachment disorganization is caused by frightened and frightening (FR) parental behavior, which is believed to have its origins in unresolved parental trauma. Maltreating behaviors are arguably among the most frightening parenting behaviors, placing children in an irresolvable paradox in which their attachment figures are simultaneously their source of safety and their source of fear (Hesse & Main, 2006).

Genetic variation also has been explored as a contributor to the development of disorganized attachment; however, little consistent evidence has emerged for a candidate gene main effect on attachment disorganization (see Luijk et al., 2011). Among maltreated children, Cicchetti, Rogosch, and Toth (2011) found that neither the serotonin transporter gene (5-HTT) nor the dopamine receptor D4 gene (DRD4) were associated with disorganized attachment. They concluded that the anomalous aspects of maltreating parenting may be so robust that they overpower the potential effect of genetic variation in the etiological pathway to attachment disorganization (Cicchetti et al., 2011).

Although attachment is conceptualized as an important stage-salient developmental task during the first year of life, attachment security continues to exert its influence on development across the life span. First, substantial stability in insecure and disorganized patterns of attachment have been observed among maltreated children (Barnett, et al., 1999). Second, disorganized attachment initiates a maladaptive trajectory that heightens the risk for future relational dysfunction, as well as various forms of psychopathology (Hesse & Main, 2006). In a recent 22-year longitudinal investigation of the influence of early infant attachment to mother on emotion regulation in adulthood, attachment status at 18 months predicted neural responding during the regulation of positive affect 20 years later (Moutsiana et al., 2014). These findings demonstrate the powerful influence that early disturbances in attachment can exert across the life span.

DEVELOPMENT OF AN AUTONOMOUS SELF

The development of an integrated sense of self typically occurs in the toddler and preschool years, arising from the successful resolution of previous stage-salient tasks, such as the formation of a secure attachment relationship. Early caregiving experiences serve as the basis for the development of representational models of the attachment figure, as well as corresponding and coherent representational models of the self and of the self in relation to others (Sroufe & Fleeson, 1986). As discussed already, many maltreated infants fail to develop an organized pattern

of attachment, increasing the probability of subsequent perturbations in representational development. Indeed, maltreated children show disruptions in many aspects of the self system.

Aberrations in self-development have been observed as early as 18 months of age, as demonstrated by investigations of visual self-recognition. On the mirror-rouge paradigm, an assessment of the presence of a cognitive self, maltreated and nonmaltreated children are comparable in their capacity to recognize themselves; however, differences emerge with respect to their affective responses (Schneider-Rosen & Cicchetti, 1991). Specifically, maltreated toddlers are more likely than nonmaltreated comparison children to display neutral or negative emotions upon seeing their images in a mirror, which may be interpreted as reflecting negative feelings about the self.

In a longitudinal study of mother–child play and emerging social behavior among infants from maltreating and nonmaltreating families, no group differences were found in infants' play maturity at 13 or 28 months. However, infants from abusing families demonstrated more imitative play than infants from nonmaltreating families, and engaged in less independent play than infants from neglecting and nonmaltreating families, suggesting a delay in emerging social behaviors. At 28 months, once again there were no differences among the groups of children from abusing, neglecting, or nonmaltreating families in child play maturity. However, children from abusing families again engaged in less child-initiated play than the children from neglecting or nonmaltreating families. Evidence that toddlers from abusing families continued to demonstrate less autonomous and self-initiated behaviors suggests that it would be important for early intervention efforts to concentrate on supporting child autonomy and facilitating maternal autonomy support among abusing families (Valentino, Cicchetti, Rogosch, & Toth, 2011).

At 30 months of age, maltreated children demonstrate disruptions in their development of an internal-state lexicon. Even after controlling for receptive vocabulary, maltreated toddlers produce proportionately fewer internal state words, show less differentiation in their attributional focus, and are more context-bound in their use of internal-state language than nonmaltreated comparisons (Beeghly & Cicchetti, 1994). In particular, maltreated children appear to be most reluctant to talk about their negative internal states (Beeghly & Cicchetti, 1994). This result is corroborated by findings that maltreated children may actually inhibit negative affect, especially in the context of their relationships with their caregivers (Lynch & Cicchetti, 1991). Maltreated children may adopt a strategy designed to suppress the expression of their own negative feelings to avoid eliciting adverse responses from their caregivers. Although this approach may be adaptive in the context of a maltreating relationship, it can become maladaptive and lead to social incompetence in other interpersonal contexts. Additionally, the inability of maltreated children to identify and discuss their own distress may play a major role in these children's difficulties in displaying empathy toward their peers.

Negative self-system processes continue to be evident in the preschool period. Maltreated children's narrative representations of parents and of self are more negative than those of nonmaltreated children (Toth, Cicchetti, Macfie, Maughan, & Vanmeenen, 2000). With respect to maltreatment subtype, neglected children have been found to tell narratives containing more negative self-representations than nonmaltreated children, whereas physically abused children possess more grandiose self-representations. These variations by subtype may reflect differences in maltreating experiences. For example, grandiose self-representations may reflect a coping process to maintain personal control in an adverse and threatening home environment, while negative self representations may develop from the chronic absence of attention and validation in a neglecting home (Toth et al., 2000). In a recent investigation of the mediating role of self-system processes in physically abused 4–7-year-old children, subgroups of abused children that differed in their internal working models of relationships were identified (Hawkins & Haskett, 2014). Moreover, these differences were related to child adjustment, with children who had more positive and fewer negative representations evidencing fewer internalizing or externalizing behavior problems.

Maltreated children also show delays in the development of false belief understanding, an important aspect of theory of mind (ToM; Cicchetti, Rogosch, Maughan, Toth, & Bruce, 2003). The onset of maltreatment during the toddler period and physical abuse were the features of maltreatment associated with delay in the development of false belief understanding. The centrality of the relation between maltreatment during the toddler period and ToM deficits flows from the importance of self-development for false belief understanding. Internal state language, increased individuation and self-other differentiation, advances in language, conceptual development, and symbolic maturity, and the development of self-conscious emotions all occur during early childhood. Maltreated youngsters manifest difficulties in these aspects of self-development, each of which is a precursor of ToM development. Thus, harsh caregiving, especially early in a child's life, impairs the development of ToM abilities.

Research among school-age maltreated children provides further evidence of self-system deviation. Relative to teacher ratings, younger maltreated children overestimate their own sense of social competence and peer acceptance (Vondra, Barnett, & Cicchetti, 1989). These children may be engaging in defensive processing to increase their sense of competence. In fact, research indicates that the development of a grandiose self, as reflected by inflated social self-efficacy, may serve as a protective factor in the link between maltreatment and internalizing symptomatology (Kim & Cicchetti, 2003). However, as maltreated children mature, they tend to underestimate their competence and are rated by teachers as having lower self-esteem (Vondra et al., 1989).

In another examination of self-system processes in maltreated children, Bennett, Sullivan, and Lewis (2010) studied shame proneness in child neglect. Shame is a highly negative and psychically painful state in which the individual perceives the entire self as defective.

Bennett et al (2010) found that neglected children reported more shame proneness and more depressive symptomatology than nonmaltreated comparison children. Prior investigations of heterogeneous groups of physically abused, sexually abused, and neglected children found elevated levels of shame. Thus, the finding of Bennett et al (2010) extended work on shame to a group of neglected children and are consistent with the results of these earlier studies.

Finally, maltreated children are at risk for developing dissociative features and disorders, perhaps the most severe deficit in the integration of the self (Macfie, Cicchetti, & Toth, 2001a, 2001b; Toth, Pickreign Stronach, Rogosch, Caplan, & Cicchetti, 2011; Valentino, Cicchetti, Rogosch, & Toth, 2008). The link between maltreatment and dissociation has been observed across a wide age range, from preschoolers to adults. Among preschoolers, physical and sexual abuse appear to be most robustly related to dissociative features, with physical abuse emerging as particularly salient for the development of dissociation at clinical levels. Furthermore, longitudinal research indicates that fragmentations in self-organization have been found in sexually abused adolescent girls, who demonstrated deviant splitting between both positive and negative self-references (Calverley, Fischer, & Ayoub, 1994).

PEER RELATIONSHIPS

Consistent with an organizational perspective on development, it has been theorized that the negative relational patterns acquired in a maltreating environment become incorporated into the structures that are pertinent for successful peer relations. Within the context of their early caregiving experiences, maltreated children may develop negative expectations regarding the self and others, as well as a concept of relationships as involving victimization and coercion. These internalizations lead to the selection and structuring of later social interactions, such that familiar relationship patterns are recreated and validated (Sroufe & Fleeson, 1986). Research supports this conceptualization of continuity in relational functioning, as maltreated children have been shown to exhibit a broad range of difficulties in the peer domain.

With regard to peer relations, maltreated children appear to traverse one of two general developmental pathways: (1) withdrawal from peer interactions; or (2) heightened aggression toward peers. In addition to these two generally diverging pathways, a subgroup of maltreated and nonmaltreated children has been identified who demonstrate both aggressive and withdrawn behaviors (Rogosch & Cicchetti, 1994). Among maltreated children, those who evidence high aggression and high withdrawal demonstrate lower social effectiveness than is the case for nonmaltreated youngsters. This unusual pattern of interaction with peers is consistent with the attachment history of maltreated children, which may be related to disorganized representational models and may result in disturbances in social encounters. By revealing indications of a response predisposition to both fight and flight, maltreated children's interactions with peers lends support to the notion that these children have internalized both sides of their relationships with their caregivers (Troy & Sroufe, 1987). Thus, maltreated children's representational models may have elements of both the victim and the victimizer, and these models may be enacted in their peer relationships. The link between maltreatment and aggressive behavior is particularly robust (e.g., Cullerton-Sen et al., 2008; Shields & Cicchetti, 2001). Moreover, aggression appears to largely account for the association between maltreatment and peer rejection (Bolger & Patterson, 2001).

Maltreatment also places children at risk for being victimized by their peers. Schwartz and colleagues (1997) demonstrated that abusive family treatment predicted boys' status as aggressive victims. In an investigation of bullying and peer victimization that included both boys and girls, Shields and Cicchetti (2001) found that maltreated children were more likely than nonmaltreated children to bully other children and more likely to be victimized by their peers. Gender did not act as a moderator, suggesting that maltreated boys and girls are at comparable risk for bullying and victimization (Shields & Cicchetti, 2001).

The effects of maltreatment on disrupted peer group functioning may be explained by perturbations in cognitive

and emotional processes. With regard to social information processing, physically abused children make errors in encoding social cues, exhibit biases toward attributing hostile intent, generate more aggressive responses, and positively evaluate aggression as an appropriate response (Teisl & Cicchetti, 2008). These deficits, in turn, mediate the association between physical abuse and aggression in the peer context. Whereas maladaptive social cognition emerges as a salient explanatory factor for physically abused children, emotion dysregulation appears to play an integral role in the link between maltreatment and aggression for all maltreated groups. Poor emotion regulation also mediates the association between maltreatment and victimization by peers (Shields & Cicchetti, 2001; Teisl & Cicchetti, 2008).

In addition to their difficulties in the larger peer group, maltreated children demonstrate weaknesses in developing and maintaining friendships (Parker & Herrera, 1996). Maltreated children report less caring and validation and more conflict and betrayal in their friendships than nonmaltreated children. In an observational setting, Parker and Herrera (1996) found that friendship dyads containing a physically abused adolescent displayed more conflict and less intimacy than dyads without an abused adolescent. Alternatively, having friends may serve as an important buffer for maltreated children against feelings of loneliness, low self-esteem, and victimization by the larger peer group.

ADAPTATION TO SCHOOL

Adaptation to school represents the major extra-familial environment in which children are exposed to a novel group of unfamiliar peers and adults. As such, it presents both a challenge to functioning and an opportunity to break free of patterns that have been established within a maltreating home. However, because an organizational perspective suggests that children's experiences in the home provide a foundation on which future transitions are built, probabilistically children who have been maltreated are at risk for failure in the school environment.

Abused and neglected children are at considerable risk for academic failure (Eckenrode, Laird, & Doris, 1993). Maltreated children perform worse on standardized tests, achieve lower grades, and are more likely to repeat a grade. Furthermore, they score lower on tests that assess cognitive maturity. Several studies have found that maltreated children have an increased risk of attaining lower levels of educational achievement and intellectual performance, as well as higher rates of truancy, school expulsion, and grade retention (Lansford, Dodge, et al., 2002; Perez & Widom, 1994). However, it is unclear whether these difficulties can be attributed to cognitive or motivational issues. With regard to motivation, Aber and Allen (1987) proposed that effectance motivation, which is the intrinsic desire to deal competently with one's environment, and successful relations with novel adults are important factors related to children's ability to adapt to their first major out-of-home environment. As such, they defined the concept of secure readiness to learn, as characterized by high effectance motivation and low dependency, as a representation for the ability to establish secure relationships with adults while feeling free to explore and engage in the environment in ways that promote cognitive development. Maltreated children score lower on secure readiness to learn than do nonmaltreated children, which is consistent with what one might expect given the insecurity or atypicality that pervades maltreated children's attachment histories. In efforts to identify those factors that might further mitigate against the impact of abuse on school performance, Trickett, McBride-Chang, and Putnam (1994) conducted an investigation with adolescent girls who had been sexually abused. Previous abuse was found to predict poorer social competence, impaired competence in learning, and lower overall academic performance. Higher levels of anxious depression, bizarre destructiveness, and dissociation were also present in victims of sexual abuse. Importantly, cognitive ability and perceived competence emerged as mediators of overall academic performance and achievement, whereas dissociative and destructive behaviors exacerbated the children's level of school success. Okun, Parker, and Levendosky (1994) also sought to examine the independent and interactive effects of physical abuse, recent exposure to additional life events such as death or illness, and social disadvantage on children's social, cognitive, and affective adjustment during middle childhood. Abused children were found to evidence difficulties in three areas: peer adjustment, self-perception, and depression. Further analyses identified unique effects of negative events and socioeconomic disadvantage on children's adjustment. Additive contributions of abuse status and socioeconomic disadvantage also predicted behavior problems at school and in the home.

In yet another investigation of links between relationship patterns and school adaptation, Toth and Cicchetti (1996) found that the security that a child experienced in relation to his or her mother, in interaction with maltreatment status, significantly affected school functioning. Nonmaltreated children who reported secure patterns of relatedness to their mothers exhibited less externalizing

behavior problems, more ego resilience, and fewer school risk factors (e.g., poor attendance, poor achievement test performance, suspensions, failure in 50% of courses, and grade retention) than did maltreated children who reported insecure patterns of relatedness. Moreover, nonmaltreated children with secure patterns of relatedness to their mothers exhibited more positive school adaptation than did nonmaltreated children who reported insecure patterns of relatedness.

In an investigation of more than 200 low-income children, impairments in academic engagement, social skills, and ego resiliency were found to be present in children with histories of maltreatment (Shonk & Cicchetti, 2001). Maltreated children manifested multiple forms of academic risk and exhibited more externalizing and internalizing behavior problems. The effects of maltreatment on academic adjustment were partially mediated by academic engagement, while maltreatment's effects on behavior problems were fully mediated by social competencies and ego resiliency.

Lansford et al. (2002) conducted a 12-year prospective study of the long-term consequences of early childhood physical maltreatment on academic, behavioral, and psychological problems in adolescence. These investigators found that adolescents who were maltreated early in life were absent from school more often and were less likely to anticipate attending college compared with nonmaltreated adolescents. Maltreated adolescents also exhibited higher levels of aggression, anxiety/depression, social withdrawal, dissociation, PTSD symptoms, and thought problems than those evidenced by nonmaltreated adolescents. The participants in the Lansford et al. (2002) study were recruited from a randomly selected sample of children from the community. The results of the Lansford et al. (2002) investigation demonstrate that undetected maltreatment in adolescents who are not receiving protective services warrants identification and intervention.

Finally, Manly, Oshri, Lynch, Herzog, and Wortel (2013) examined the impact of child neglect during the first 4 years of life on adaptation to school during kindergarten and first grade in the context of neighborhood poverty (NP). Processes related to the development of school competencies were examined, including the mediational role of cognitive functioning and ego-resiliency (ER) in shaping children's school outcomes. A total of 170 low-income urban children were followed prospectively for 2 years (ages 4–6). Results indicated that neglected children had significantly lower scores on kindergarten classroom behavior and first-grade academic performance than nonneglected children. Children's cognitive performance at age 4, controlling for maternal intelligence quotient, mediated the relation between severity of neglect and children's behavior in kindergarten as well as their academic performance in first grade. Moreover, severity of neglect was related to children's ER at age 4. However, additional ecological adversity in the form of NP moderated the link between ER and classroom behavior, such that at lower levels of poverty, ER mediated the relation between severity of neglect and school adaptation. Conversely, when NP was extreme, the effects of ER were attenuated and ER ceased to predict behavioral performance in kindergarten. Preventive interventions should focus on reducing the occurrence of child neglect as well as assisting families with promoting cognitive and coping skills when children have experienced neglect. Ameliorating negative environments for children in extreme poverty also is critical to reduce risks of school failure.

Now that we have addressed stage-salient aspects of the sequelae of maltreatment, we next direct our attention toward memory, personality organization, and molecular genetic and neurobiological domains.

EFFECTS OF MALTREATMENT ON MEMORY

There are a number of reasons why maltreatment might be expected to alter basic memory processes (Howe, Cicchetti, & Toth, 2006). For example, the experience of stress associated with living in a maltreating home may potentiate neurological changes in the structures implicated in encoding and storing information. Observed delays in intellectual functioning, executive functioning, and language may also play roles in potential memory deficits. Furthermore, maltreated children are at risk for the development of posttraumatic stress disorder (PTSD) and dissociation, both of which have been linked to memory distortion among adults.

For the most part, hypothesized adverse effects of maltreatment on memory have not been empirically supported. Although the field is still in its infancy, many studies show no differences between maltreated and nonmaltreated children in terms of basic memory processes. Maltreated children are comparable to their nonmaltreated peers with respect to basic recall and recognition, as well as in their degree of suggestibility to misinformation (Eisen, Goodman, Qin, Davis, & Crayton, 2007; Howe, Cicchetti, Toth, & Cerrito, 2004; Porter, Lawson, & Bigler, 2005). Moreover, Beers and DeBellis (2002) did not find any differences in basic memory processes between maltreated children with PTSD and normative comparison youth.

Similarity in memory functioning is evident in studies involving both neutral and emotionally laden stimuli (Howe et al., 2004; Howe, Toth, & Cicchetti, 2011). In addition, differences in memory processes fail to emerge with respect to ecologically valid and stressful information (Eisen et al., 2007). For example, Eisen and colleagues (2007) tested memory for an ano-genital exam that occurred in the context of an inpatient abuse assessment. Memory accuracy and suggestibility did not vary by abuse status.

Although no between-group differences have been discovered, within-group investigations suggest variation in basic memory processes as a function of maltreatment subtype (Toth & Cicchetti, 1998). For example, in a depth-of-processing incidental recall task of self-referent information, neglected children demonstrated a greater proportion of negative false recall and less positive false recall than did the abused children, suggesting greater memory inaccuracy among neglected children (Valentino, Cicchetti, Rogosch, & Toth, 2008). In another study by Valentino, Cicchetti, Rogosch, and Toth (2008), subtype differences emerged for memory of maternal-referent information, such that abused children exhibited lower recall compared with neglected children. These findings are suggestive of defensive processing of information that activates the attachment system as a protective mechanism among abused children. Relatedly, Lynch and Cicchetti (1998b) examined the links among trauma, representational models of caregivers, and children's memory for mother-referent information. Results were consistent with the hypothesis that experiences of trauma and representational models of caregivers are associated with differences in the way children process and retrieve information about positive and negative mother-attribute words. Specifically, victimized children with insecure representational models of their caregivers recalled the highest proportion of negative mother stimuli. Finally, Cicchetti, Rogosch, Howe, and Toth (2010) showed that children with a history of neglect and/or emotional maltreatment and low cortisol evinced increased levels of memory inaccuracy.

In addition to subtype differences in basic memory processes, Valentino et al. (2009) revealed subtype-specific variation in autobiographical memory for nontraumatic events. Abused children's memories were more overgeneral than the memories of neglected and nonmaltreated children. Retrieving memory in generic form may reflect a strategy for avoiding negative affect associated with painful memories. Consistent with a dynamic skills framework, defensive, traumatogenic responses become more habitual and generalized over time, resulting in less integration of memories.

PERSONALITY ORGANIZATION AND PSYCHOPATHOLOGY

Child maltreatment ushers in motion a probabilistic path of epigenesis for abused and neglected children that often results in a profile of relatively enduring vulnerability factors that increase the probability of the emergence of maladaptation and psychopathology. Indeed, consistent with the concept of multifinality, maltreated children develop a broad range of psychopathological outcomes.

In general, the literature indicates that exposure to child maltreatment increases the risk for greater lifetime prevalence of high levels of many psychopathological symptoms and disorders (Scott, Smith, & Ellis, 2010). These include, but are not restricted to, mood and anxiety disorders (Kim & Cicchetti, 2006; Widom, DuMont, & Czaja, 2007), dissociation and suicidal behavior (Yates, Carlson, & Egeland, 2008), substance use disorders (Rogosch, Oshri, & Cicchetti, 2010; Widom, Marmorstein, & White, 2006), disruptive and antisocial behaviors (Egeland, Yates, Appleyard, & van Dulmen, 2002; Widom & Maxfield, 2001) and psychosis (Arseneault et al., 2011; Toth, Pickreign Stronach, Rogosch, Caplan, & Cicchetti, 2011).

Toth, et al. (2011) conducted the first prospective investigation that demonstrates the deleterious consequences of maltreatment on children's ability to think coherently. Maltreated and nonmaltreated school-age children individually participated in a story game designed to elicit speech samples. Children were instructed to listen to two recorded stories and prompted to retell the stories. Children were then asked to create their own story from possible topics. Maltreated children exhibited more illogical thinking than nonmaltreated children, and the level of illogical thinking in maltreated children was in the clinically pathological range. The occurrence of multiple subtypes of maltreatment and the chronicity of the maltreatment also were associated with illogical thinking. Although interventions provided to maltreated children typically address behavior problems and maladaptive cognitive processing, less attention is directed toward ascertaining whether the thinking of these children reflects actual thought distortions. Efforts to assess illogical thinking and to intervene to modify these patterns before they become more consolidated might ultimately help to decrease the risk for future serious psychopathology, including bipolar disorder and schizophrenia.

Longitudinal research by Kaplow and Widom (2007) suggests that the age of onset of maltreatment may be an important factor in differentiating the effects of maltreatment on later mental health outcomes. In particular, individuals who were maltreated earlier in life (i.e., before the age of 6 and/or during the infancy or preschool years) evinced higher levels of internalizing problems as adults, whereas those who were older at the time of maltreatment went on to develop more externalizing outcomes in adulthood. The preschool years emerged as a potential sensitive period during which maltreatment may have an especially robust effect, potentiating the development of both internalizing and externalizing disorders (i.e., anxiety, depression, antisocial personality disorder).

Rogosch, Oshri, and Cicchetti (2010) tested a longitudinal developmental cascade model of associations among child maltreatment, internalizing and externalizing psychopathology, social competence, and cannabis abuse and dependence (CAD) symptoms. Children were assessed at four developmental periods: age 7 to 9, 10 to 12, 13 to 15, and 15 to 18. Results indicated significant paths from child maltreatment to early externalizing and internalizing problems and social competence, as well as to CAD symptoms in adolescence. Youth CAD symptoms were primarily related directly to child maltreatment and externalizing problems. Childhood internalizing symptoms contributed to later childhood decreases in social competence, which predicted increases in later externalizing problems.

In a longitudinal investigation, Oshri, Rogosch, and Cicchetti (2013) found that a personality typology derived from the California Q-set Items representative of ego resiliency and ego control (Block & Block, 1969, Block & Block, 1980) was associated with child maltreatment and predicted adolescent psychopathology. Maltreated children were significantly more likely than nonmaltreated children to be classified in the overcontrolled and undercontrolled profiles compared with the resilient profile. The undercontrolled profile reported higher cannabis symptoms and externalizing problems in adolescence than the other two profiles. The overcontrolled group showed the highest levels of internalizing and lowest levels of alcohol problems compared with the other profiles. Person-centered mediation analyses showed that the overcontrolled and the undercontrolled profiles significantly and differentially mediated the link between number of child maltreatment subtypes and the development of adolescent psychopathology.

Manly, Kim, Rogosch, and Cicchetti (2001) found that the severity of emotional maltreatment in the infancy and toddlerhood period and physical abuse during the preschool period predicted externalizing behavior and aggression. Severity of physical neglect, particularly when it occurred during the preschool period, was associated with internalizing symptomatology and withdrawn behavior. Additionally, maltreatment during the school-age period contributed significant variance after earlier maltreatment was controlled. Chronic maltreatment, especially with onset during infancy and toddlerhood or preschool periods, was linked with more maladaptive outcomes (Manly et al., 2001). The significance of chronic maltreatment attests to one of the tenets of the organizational perspective on development, in terms of links between adversity across multiple developmental periods and detrimental impact on later functioning. An examination of the interplay among developmental timing, severity, and subtype in relating to adaptation of maltreated children in the Manly et al. (2001) study provided a more clearly delineated picture of multifinality of outcomes within the phenomenon of maltreatment than a global categorization could provide.

Keiley, Howe, Dodge, Bates, and Pettit (2001) conducted a longitudinal study from kindergarten (roughly, ages 4 to 5) through eighth grade (age 12). Growth modeling was used to determine the developmental trajectories of mother-reported and teacher-reported internalizing and externalizing behaviors for two groups of physically abused children—early-harmed (pre-age 5), later-harmed (after age 5) and a group of nonharmed children. Children who experienced early physical harm from significant adults in their lives were more likely to experience adjustment problems in early adolescence. Over multiple domains, early physical maltreatment was related to more negative sequelae than the same type of maltreatment occurring at later periods. In addition, the fitted growth models revealed that the early-harmed group exhibited somewhat higher initial levels of teacher-reported externalizing problems in kindergarten and significantly different rates of change in these problem behaviors than other children, as reported by mothers over the 9 years of this study. The early-harmed children also were seen by their kindergarten teachers as exhibiting higher levels of internalizing behavior. The later-harmed children were seen by their teachers as increasing their externalizing problem behaviors more rapidly over the 9 years than did the early- or nonharmed children. Like those of Manly et al. (2001), these findings indicate that the timing of maltreatment is a salient factor in examining the developmental effects of physical harm.

Maltreatment has also been implicated in the etiology of personality disorders. Given that personality disorders do not emerge spontaneously at the age of 18, the age

cutoff established in the psychiatric nomenclature, some researchers have adopted a developmental psychopathology approach by seeking to identify early precursors and processes that confer vulnerability to later personality pathology (Cicchetti & Crick, 2009). Consistent with this approach, Rogosch and Cicchetti (2005) found that maltreated children exhibit higher mean levels of potential precursors to borderline personality disorder (e.g., emotional lability, conflictual relationships with adults and peers, relational aggression, self-harm) than do nonmaltreated comparisons. Bemporad, Smith, Hanson, and Cicchetti (1982); Hecht, Cicchetti, Rogosch, and Crick (2014); Widom, Czaja, and Paris (2009); and Zanarini (2000), among others, have found that maltreatment is associated with higher levels of borderline personality symptoms. An examination of early risk factors for paranoid personality identified a history of child maltreatment as a predictor, alongside significant behavioral disturbances and negative peer relationships (Natsuaki, Cicchetti, & Rogosch, 2009). In a prospective investigation of personality organization, Rogosch and Cicchetti (2004) found that 6-year-old maltreated children exhibited lower agreeableness, conscientiousness, and openness to experience, as well as higher neuroticism than did nonmaltreated children. Analysis of personality clusters revealed that the majority of nonmaltreated children were represented in the adaptive Gregarious and Reserved personality clusters, whereas maltreated children largely accounted for the makeup of less adaptive personality profiles (i.e., undercontroller, overcontroller, and dysphoric). Furthermore, longitudinal stabilities were observed across ages 7, 8, and 9, suggesting continuity in maltreated children's personality liabilities.

GENE–ENVIRONMENT INTERACTION

Research in molecular genetics suggests that maltreated children's risk for psychopathology is not inevitable. GxE occurs when the effect of exposure to an environmental factor on a behavioral, health, or biological phenotype is conditional upon a person's genotype or, conversely, when the genotype's effect is moderated by the environment (Moffitt, Caspi, & Rutter, 2005). In the past decade, our understanding of the role of the environment and its interaction with genes has been further clarified, with reciprocal coactions between the environment and the individual resulting in differential expression of genetic material. Environmental conditions may interact with an individual's genetic makeup to alter processes such as the timing of the initiation of transcription and translation for a specific gene, the direction for which it does so, or whether the gene will ultimately be expressed.

In a landmark epidemiological study, Caspi and colleagues (2002) followed a large sample of male children from birth to adulthood to ascertain why some maltreated children grow up to develop antisocial personality disorder, whereas others do not. Results revealed that a functional polymorphism in the promoter of the monoamine oxidase A (MAOA) gene moderated the effect of child maltreatment. The MAOA gene is located on the X chromosome and encodes the MAOA enzyme, which metabolizes neurotransmitters such as norepinephrine, serotonin, and dopamine, rendering them inactive. Maltreated children with the genotype conferring high MAOA activity were significantly less likely to develop antisocial behavior problems than maltreated children with the low MAOA-activity genotype. In addition, maltreatment and nonmaltreatment groups did not differ on MAOA activity, suggesting a lack of an evocative gene-environment correlation as an explanation for the GxE findings. Many, but not all, subsequent studies have been successful in replicating Caspi et al.'s original findings and in extending them downward to samples of children and adolescents (Kim-Cohen et al., 2006).

Byrd and Manuch (2014) conducted a meta-analysis of studies testing the interaction of MAOA genotype and childhood genotype on antisocial outcomes in predominantly nonclinical samples. Consistent with the findings of Caspi et al. (2002), for males early maltreatment predicted antisocial outcomes more strongly for low-activity, relative to high-activity, MAOA genotype. In contrast, for females MAOA did not interact with early life adversities, whereas maltreatment alone predicted antisocial behaviors in females who had the high-activity MAOA genotype.

In another seminal study, Caspi et al. (2003) examined the prospective link between maltreatment and depression. Caspi et al. (2003) found that genetic variation in a functional polymorphism (5-HTTLPR) in the promoter region of the serotonin transporter gene (5-HTT) plays a moderating role. The particular serotonin gene variants (s/s, s/l, and l/l) affect the amount of serotonin transporter protein that is produced. The serotonin transporter is a protein that is critical to the regulation of serotonin function in the brain, through terminating the action of serotonin in the synapse via reuptake. The serotonin transporter gene plays a pivotal role in brain development and in individual differences in mood and behavioral regulation. Thus, 5-HTTLP was an excellent candidate gene for Caspi et al.'s (2003) research. Adults carrying the *s* allele (s/s or s/l) were

found to exhibit more depressive symptoms, diagnosable depression, and suicidality in response to stressful life events than individuals homozygous for the l (l/l) allele. In addition, an examination of early life stress showed that a history of child maltreatment predicted depression in adulthood, but only among *s* carriers.

Whereas work in behavior genetic and in molecular genetic research using genome-wide association studies did not examine GxE, the Caspi et al. (2002, 2003) investigations generated much excitement because they suggested that the combination of molecular genetic elements and well-measured environments and phenotypes could not only increase our understanding of the development of psychopathology, but also uncover additional genes that play roles in the etiology of psychopathology that would not have been discovered in main effects molecular genetic studies. GxE research, however, has not been without critics (Duncan & Keller, 2011; Duncan, Pollastri, & Smoller, 2014; Hewitt, 2012; Keller, 2014). Some of the most notable emanated from the findings of the meta-analysis conducted by Risch et al. (2009) in which they concluded that 5-HTTLPR does not moderate the relation between stress and depression in contrast to the findings of Caspi et al. (2003).

In response, Caspi et al. (2010) evaluated multiple lines of evidence for the 5-HTT stress-sensitivity hypothesis. The evidence was drawn from experimental neuroscience, nonhuman primate research, and studies of genetically engineered 5-HTT mutations in rodents and dispels some misconceptions about GxE research. Relatedly, Karg, Burmeister, Shedden, and Sen (2011) critically reviewed two meta-analyses that examined the interaction between 5-HTTLPR and stress in the development of depression (Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). Contrary to Risch's meta-analysis, Karg and colleagues (2011) found strong evidence in support of the hypothesis that 5-HTTLPR moderates the relationship between stress and depression.

We next selectively review GxE research on maltreated children, adolescents, and adults who report having experienced maltreatment in their childhoods. We focus on studies that examined the most commonly studied candidate genes in GxE research on child maltreatment, namely 5-HTTLPR, corticotropin releasing hormone receptor gene (CRHR1), and MAOA.

Kaufman et al. (2004) found that maltreated children with the s/s genotype of 5-HTTLPR evinced depression scores that were almost twice as high as the depression scores of maltreated children with the s/l and l/l genotypes. Kaufman et al. (2006) replicated these findings in a subsequent study, the results of which revealed a significant three-way interaction between brain derived neurotrophic factor (BDNF) genotype, 5-HTTLPR, and maltreatment in predicting heightened levels of depression. (see also Grabe et al., 2012, for similar results). In another instance of gene–gene–environment interaction (GxGxE), Cicchetti, Rogosch, and Sturge-Apple (2007) found that adolescents with a history of sexual abuse who carried both the s/s genotype and the low MAOA-activity genotype evinced higher levels of depression symptomatology than sexually abused adolescents with alternative combinations of the variants of the 5-HTT and MAOA genes.

Cicchetti and Rogosch (2014) examined genetic moderation of the effects of child maltreatment on depression and internalizing symptoms in a large sample of 7- to 12-year-old (mean age—10) low-income maltreated and nonmaltreated African American children (N = 1,096). Lifetime child maltreatment experiences were independently coded from Child Protective Services records and maternal report. Child depression and internalizing problems were assessed in the context of a summer research camp by self-report on the Children's Depression Inventory and adult counselor report on the Teacher Report Form. DNA was obtained from buccal cell or saliva samples and genotyped for polymorphisms of the following genes: serotonin transporter linked polymorphic region (5-HTTLPR), brain-derived neurotrophic factor (BDNF), norepinephrine transporter, and corticotropin releasing hormone receptor 1. Analyses of covariance with age and gender as covariates were conducted with maltreatment status and respective polymorphism as main effects and their GxE interactions. Maltreatment consistently was associated with higher Children's Depression Inventory and Teacher Report Form symptoms. The results for child self-report symptoms indicated a GxE interaction for BDNF and maltreatment (cf. Kaufman et. al., 2006). In addition, BDNF and triallelic 5-HTTLPR interacted with child maltreatment in a GxGxE interaction. Analyses for counselor report of child anxiety/depression symptoms on the Teacher Report Form indicated moderation of child maltreatment effects by triallelic 5-HTTLPR. These effects were elaborated based on variation in developmental timing of maltreatment experiences. Norepinephrine transporter was found to further moderate the GxE interaction of 5-HTTLPR and maltreatment status, revealing a GxGxE interaction. This GxGxE was extended by consideration of variation in maltreatment subtype experiences. Finally, GxGxE effects were observed for the co-action of BNDF and the corticotropin releasing hormone receptor 1 haplotype. The findings illustrate the variable influence

of specific genotypes in GxE interactions based on variation in maltreatment experiences and the importance of a multigenic approach for understanding influences on depression and internalizing symptoms among African American children.

Differential pathways may suggest implications for preventing depression in African American children and for intervening with individuals where depression has occurred. Depression among African Americans children and adolescents is an important public health concern (Byck, Bolland, Dick, Asbeck, & Mustanski, 2013). In addition, distressed African American youth are less likely to receive treatment (Carson, Cook, & Alegria, 2010; Kodjo & Audinger, 2004). Moreover, racial discrimination contributes to the development of depressive symptoms (English, Lambert, & Ialingo, 2014). Thus cultural considerations will be important in any intervention initiatives. The design and implementation of effective intervention approaches will be advanced by attention to the diversity of multilevel processes involved in differential pathways to depressive outcomes among African American children and adolescents.

Banny, Cicchetti, Rogosch, Oshri, and Crick (2013) examined child maltreatment, peer victimization, and 5-HTTLPR as predictors of depressive symptomatology. Path analyses revealed that both relational and overt victimization mediated the association between child maltreatment and depressive symptoms. Bootstrapping procedures used to test moderated-mediation demonstrated that genotype moderated the indirect effects of relational and physical victimization on child depressive symptoms, such that victimized children with the l/l genotypic variant of 5-HTTLPR were at increased risk for depressive symptoms compared with victimized children carrying a short allele.

A number of investigations have demonstrated that individuals who had been maltreated possessed a significantly greater risk of experiencing suicidal behaviors (i.e., suicidal ideation; suicide attempts; completed suicide) than comparable samples of nonmaltreated persons from the same socioeconomic status. These studies have demonstrated that the experience of sexual and physical abuse are significant risk factors for suicidal behaviors in adolescents and adults (Brodsky & Stanley, 2008). Cicchetti, Rogosch, Sturge-Apple, and Toth (2010) investigated whether genotypic variation of 5-HTTLPR moderated the effect of maltreatment on suicidal ideation in a sample of low-income maltreated and nonmaltreated school-age children. Higher suicidal ideation was found among maltreated than nonmaltreated children. Children with one to two maltreatment subtypes and s/s or s/l genotypes had higher suicidal ideation than those with the l/l genotype; suicidal ideation did not differ in nonmaltreated children or in children with three to four maltreatment subtypes based on 5-HTTLPR variation. Results were applicable to emotionally maltreated/neglected and to physically abused/sexually abused children. Interestingly, for the more extensively maltreated (i.e., those with three to four subtypes), children expressed higher levels of suicidal ideation, irrespective of genetic variation. Thus, the pathogenic relational environment of children who experienced extensive maltreatment appears to have predominated over genotypic variation in the risk for, or protection against, suicidal ideation.

In a final illustration of 5-HTTLPR as a moderator of depression in maltreated children, Uher et al. (2011) conducted a prospective longitudinal examination of G×E interaction in two large samples, one in New Zealand, and one in England. The former sample was followed until age 32, the latter until age 40. The prospective nature of this analysis is unique in that most studies of 5-HTTLPR × maltreatment on depression have been cross sectional. Uher and colleagues (2011) found that, in both longitudinal cohorts, statistical analyses of GxE interactions revealed positive results for depression that runs a persistent course in adulthood, but not for single-episode depression. Individuals with two short 5-HTTLPR alleles and child maltreatment had elevated risk of persistent but not single-episode depression. Thus, research that does not distinguish persistent course and single-episode depression may underestimate GxE effects and could explain some of the nonreplications found in GxE research (Duncan & Keller, 2011).

CRHR1 is another gene that has been shown to be a viable candidate gene that influences vulnerability to depression. Corticotropin-releasing hormone is the key activator of the hypothalamic-pituitary-adrenal (HPA) axis, binding to receptors that initiate the stress response, culminating with release of cortisol from the adrenal cortex. Overactivity of the HPA-axis has been shown to be partially caused by hyperactivity of CRH neurons. Additionally, CRH activity at the CRH type 1 receptor (CRHR1) in extra-hypothalamic regions also are thought to bring about internalizing disorders, such as depression and anxiety (Bradley et al., 2008). Published investigations to date suggest that hyperactivity of the HPA axis may be a function of early life stress (Cicchetti, Rogosch, Gunnar, & Toth, 2010; Heim et al., 2008).

Bradley and colleagues (2008) conducted a study to test the hypothesis that genetic polymorphisms that alter

the functionality of CRHR1 may moderate the effects of child maltreatment on adult depression. These investigators found that a G×E interaction was important for the expression of depressive symptoms, or lack thereof, in adults who possess CRHR1 risk or protective alleles in conjunction with a history of child maltreatment. In keeping with Moffitt et al. (2005), the findings of Bradley et al. (2008) underscore the importance of taking the environment into account in genetic association and linkage studies that otherwise might miss many important genetic variants that are involved in the etiology of complex diseases. An extension and partial replication of the Bradley et al. (2008) study was conducted by Polanczyk et al. (2009). As in the investigation of Bradley et al. (2008), a CRHR1 haplotype was shown to exert a protective effect against depression in adults who were maltreated in their childhood; however, the replication only occurred when a retrospective, but not a prospective, measure of child maltreatment was used. The authors speculated that the protective effect of the CRHR1 haplotype was likely related to its function in consolidating memories of emotionally arousing experiences.

DeYoung, Cicchetti, and Rogosch (2011) examined the influence of CRHR1 variation on neuroticism, in interaction with child maltreatment, in a large sample of maltreated children and a well-matched nonmaltreated comparison group. Neuroticism, one of the Big Five personality characteristics, is a risk factor for mood and anxiety disorders. The biological systems involved in neuroticism are thus of great import in the etiology of internalizing disorders. Genes that are involved in the systems that are stress responsive, such as CRHR1, are thus important candidates for studies of the genetic moderation of the effects of major stressors like maltreatment.

DeYoung et al. found that the CRHR1 TAT haplotype significantly moderated the association of child maltreatment with neuroticism. Having two copies of the TAT haplotype of CRHR1 was associated with higher levels of neuroticism among maltreated children relative to nonmaltreated children, with the exception of sexually abused children and children who had experienced 3 or 4 types of maltreatment. The findings of this study are also important because they contribute to a growing body of evidence that variation in the CRHR1 gene moderates the effects of child maltreatment.

Research reviewed shows that GxE interactions mediating depressive symptomatology have been identified in both the stress-sensitive serotonergic (5-HTTLPR) and corticotropin-releasing hormone (CRHR1) systems. In an innovative investigation of African Americans of low-SES, Ressler et al. (2010) sought to determine whether the effects of child maltreatment are moderated by GxGxE interactions between CRHR1 and 5-HTTLPR polymorphisms. Ressler and colleagues first replicated the interaction of child maltreatment and 5-HTTLPR on lifetime major depressive disorder. They next replicated earlier work in their laboratory by Bradley et al. (2008), once again finding that an interaction between a CRHR1 haplotype and child maltreatment predicted current depressive symptoms. Furthermore, Ressler et al. (2010) discovered that a G (5-HTTLPR s allele) x G (CRHR1 haplotype) interaction with child maltreatment predicted current depressive symptoms.

MAOA is a mitochondrial enzyme that is expressed predominantly in catecholaminergic neurons and is responsible for the degradation of a variety of biogenic amines (Caspi et al., 2002). A well-characterized *u*-VNTR polymorphism exists in the promoter region of the MAOA gene that is known to affect gene expression. The number of tandem repeats of this polymorphism (i.e., 2, 3, 5 vs. 3, 5, 4) determines the efficiency (i.e., high activity, low activity) with which MAOA is transcribed and ultimately produced within individuals (Caspi et al., 2002).

Weder et al. (2009) examined a GxE interaction of MAOA genotype and maltreated children. The maltreated children represented the extreme on a continuum of adversity. They were assessed at a highly stressful time—shortly after they had been removed from their parents' care because they had been physically abused. A total trauma index score was derived based on inclusion of physical abuse, sexual abuse, domestic violence exposure, multiple out-of-home placements, and community violence exposure. Scores were rated from mild to moderate to extreme. Weder et al. (2008) detected a significant interaction between exposure to moderate levels of trauma and the low activity MAOA genotype in conferring increased risk for aggression. Children who were exposed to extreme levels of trauma had high aggression scores regardless of MAOA genotype. Extreme levels of trauma appear to overshadow the effects of MAOA genotype, especially during a period when traumatized children are experiencing acute stress. The findings of Weder and colleagues are consistent with those of Caspi et al. (2002).

To provide a final example, as in Caspi et al.'s (2002) original study, Cicchetti, Rogosch, and Thibodeau (2012) conducted an investigation to examine a G×E interaction of MAOA genotype and child maltreatment on early signs of antisocial behavior in school-age children. Because the MAOA gene is sex-linked and located on the X chromosome, males have one allele on the X chromosome.

In contrast, females have an MAOA allele on each X chromosome; however, only one of the alleles is active. Consequently, ambiguity results in determining which allele is active among females who are heterozygous for MAOA activity level alleles (i.e., high-low or low-high activity). Thus, analyses involving MAOA were conducted only among boys.

For lifetime antisocial behaviors, Cicchetti et al. (2012) did not find MAOA to contribute to models of antisocial behavior as reported by peers or adults beyond the influence of maltreatment effects. The GxE interaction effect was significant. Among nonmaltreated children, those with low activity MAOA genotypes had significantly higher observer-reported symptoms of antisocial behavior than those with high-activity MAOA genotypes. Moreover, maltreated children in the low-activity MAOA group had higher self-reported antisocial behavior than nonmaltreated children. A similar pattern of findings was observed for child self-report of antisocial behavior in the past 6 months, as the GxE interaction was significant. Specifically, maltreated children with low MAOA-activity genotypes had higher recent antisocial behavior than those with high activity genotypes. No significant differences were found among nonmaltreated children based on the MAOA genotype group. Furthermore, maltreated children with low MAOA activity genotypes had higher-level self-reported antisocial symptoms than nonmaltreated children. The risk for antisocial behavior associated with child maltreatment was reduced among children with high MAOA-activity genotypes. The findings of Cicchetti et al. (2012) are consistent with those reported by Caspi et al. (2002) and Weder et al. (2008) (for a meta-analysis, see Kim-Cohen et al., 2006).

Cicchetti, Rogosch, Hecht, Crick, and Hetzel (2014) conducted an investigation in which gene-environment-gender effects in predicting child borderline personality disorder among maltreated and nonmaltreated low-income children (N = 1,051) were examined. Adult-, peer-, and self-report assessments of borderline precursor indictors were obtained, as well as child self-report on the Borderline Personality Features Scale for Children. Genetic variants of the oxytocin receptor genotype and the FK506 binding protein 5 gene CATT haplotype were investigated. Children who self-reported high levels of borderline personality symptomology were differentiated by adults, peers, and additional self-report on indicators of emotional instability, conflictual relationships with peers and adults, preoccupied attachment, and indicators of self-harm and suicidal ideation. Maltreated children also were more likely to evince many of these difficulties relative to nonmaltreated children. A series of analyses of covariance, controlling for age and ancestrally informative markers, indicated significant maltreatment–gene–gender (MxGxG) three-way interactions. Consideration of the maltreatment parameters of subtype, onset, and recency expanded understanding of variation among maltreated children. The three-way interaction effects demonstrated differential patterns among girls and boys. Among girls, the gene-environment interaction was more consistent with a diathesis-stress model (Gottesman & Shields, 1972), whereas among boys a differential-sensitivity (Belsky et al., 2007; Ellis et al., 2011) interaction effect was indicated. Moreover, the genetic variants associated with greater risk for higher borderline symptomatology, dependent on maltreatment experiences, were opposite in girls compared with boys. The findings have important implications for understanding variability in early predictors of borderline personality.

MALTREATMENT AND ALLOSTATIC LOAD

In addition to GxE effects, child abuse and neglect are also implicated in the disruption of biological systems, including neuroendocrine functioning, immunological functioning, health outcomes, and neurobiology. The concepts of allostasis and allostatic load (AL) provide an integrative framework for understanding how exposure to chronic stress, such as child maltreatment, potentiates long-term liabilities for physical and mental health (Danese & McEwen, 2012). Allostasis is a process that involves the activation of multiple interactive physiological systems (e.g., HPA, sympathetic-adrenal-medullary axes, cardiovascular, immune, and metabolic systems). In the short term, mobilization of these systems exerts a protective effect on the body and promotes an adaptive response to stress; however, with chronic activation, physiological reactions to stress become less efficient in protecting the individual. Ensuing damage to the body results in allostatic overload, which, in turn, contributes to changes in brain structure and function and the development of various disease states.

Shonkoff, Boyce, and McEwen (2009) differentiated among three types of stress that children may experience. Normative and routine life challenges that are embedded within a context of protective factors, such as positive, supportive relationships, are considered tolerable stress. Alternatively, toxic stress involved conditions in which the child is exposed to chronic, severe, and prolonged stress, often occurring in the absence of protective

factors. Abuse and neglect constitute an example of toxic stressors.

Allostatic load theory suggests that an accumulation of stress-comprised regulatory processes across multiple systems provides a better global index of the degree of allostatic overload that is operating than any one system measured in isolation.

NEUROENDOCRINE REGULATION AND REACTIVITY

Cicchetti and Rogosch (2001a) examined the extent to which maltreated children vary with respect to cortisol regulation, a biomarker of AL. Although no differences in cortisol regulation were found between the maltreated and nonmaltreated groups, findings revealed significant within-group variation as a function of maltreatment subtype. In particular, children who had experienced both physical and sexual abuse, in combination with neglect and/or emotional maltreatment, exhibited substantial elevations in morning cortisol levels (i.e., hypercortisolism). In addition, a subgroup of physically abused children showed a trend toward lower morning cortisol relative to nonmaltreated children (i.e., hypocortisolism). Furthermore, the neglected and emotionally maltreated groups did not differ from nonmaltreated children in terms of cortisol regulation.

Longitudinal analysis of the developmental course of cortisol dysregulation accommodates findings of both hyper- and hypocortisolism among maltreated children. Trickett, Noll, Susman, Shenk, and Putnam (2010) measured cortisol activity at six time points spanning childhood, adolescence, and young adulthood to determine the effects of maltreatment on cortisol regulation. Although the cortisol levels of sexually abused females were initially higher compared with nonabused females, their levels were lower by early adulthood. Results support an attenuation hypothesis, whereby the HPA axis adapts to hypersecretion by down-regulating its response to stress, eventually resulting in hyposecretion.

In another longitudinal investigation, Alink, Cicchetti, Kim, and Rogosch (2012) aimed to elucidate the effect of maltreatment on social functioning and cortisol regulation over time. Results of this study suggest that maltreated children are more likely to experience difficulties in social functioning which, in turn, are related to cortisol regulation one year later.

Research investigations also have examined whether cortisol differentially relates to social and psychological functioning based on maltreatment status (see Tarullo & Gunnar, 2006, for a review). This hypothesis was supported by the findings of Cicchetti and Rogosch (2001b), which indicated that depressed maltreated children exhibited a pattern of cortisol dysregulation that was not evident among depressed nonmaltreated children. Similarly, in a later study by Cicchetti et al. (2010), children who had experienced early sexual and/or physical abuse (i.e., in the first 5 years of life) and who also had high internalizing symptoms uniquely exhibited an attenuated diurnal decrease in cortisol, whereas nonmaltreated children with high internalizing symptomatology did not evince neuroendocrine dysregulation. The findings were specific to early sexual and physical abuse rather than later onset physical and or sexual abuse or early occurring neglect or emotional maltreatment.

Trickett, Gordis, Peckins, and Susman (2014) examined the association of recent maltreatment experiences with cortisol reactivity in a large group of maltreated ($N = 303$) and nonmaltreated ($N = 151$) adolescents. Cortisol reactivity was assessed by a laboratory stressor, a modified version of the Trier Social Stress Test. Results indicated that the maltreated adolescents showed a blunted or attenuated response to the stressor as compared with those in the comparison group.

Quellet-Morin et al. (2011) found that maltreated/bullied children had lower cortisol responses than comparison children who exhibited a significant increase. Lower cortisol responses were, in turn, associated with more social and behavioral problems among maltreated/bullied children.

Tyrka et al. (2009) conducted a study to determine whether CRHR1 polymorphisms interact with child maltreatment to predict HPA-axis reactivity, which has been linked both to early life stress and to depression. Several single nucleotide polymorphisms (SNPs) of CRHR1 showed a significant interaction with maltreatment in the prediction of cortisol response to the dexamethasone (DEX) suppression test. For the adults who experienced maltreatment in their childhood, the GG genotype of each of the CRHR1 SNPs was associated with elevated cortisol responses to DEX. Tyrka et al. (2009) conjectured that excessive HPA axis activation could represent a mechanism of interaction of risk genes with stress in the development of mood disorders.

Relatedly, Cicchetti, Rogosch, and Oshri (2011), within an allostatic load framework, investigated the effect of GxE interactions on diurnal cortisol regulation and internalizing symptomatology. Variation in the CRHR1 TAT haplotype and 5-HTTLPR was identified in a sample of

maltreated and nonmaltreated children. GxE effects for CRHR1 and maltreatment and early abuse (before age 5) on diurnal cortisol regulation were observed; CRHR1 variation was related to cortisol dysregulation only among maltreated children. Early abuse and high internalizing symptoms also interacted to predict atypical diurnal cortisol regulation. The interaction of CRHR1, 5-HTTLPR, and child maltreatment (GxGxE) identified a subgroup of maltreated children with high internalizing symptoms who shared the same combination of the two genes. The findings provide support for an allostatic load perspective on the effects of the toxic stress associated with child maltreatment on cortisol regulation and internalizing symptomatology as moderated by genetic variation.

There are different models of how the effects of excesses, deficits, and dysregulation in the primary mediators of AL, particularly cortisol, may affect brain structure and function. Further, developmental considerations are important. In this regard, the timing of periods of severe stress may be critical. For example, variation in the age of maturation of brain structures, notably the hippocampus, prefrontal cortex, and the amygdala, may result in differential effects on functioning and health (Lupien, McEwen, Gunnar, & Heim, 2009; Shonkoff et al., 2009). Sensitive periods in the development of these brain structures may generate heightened vulnerability to the neurotoxic effects of excess glucocorticoids, thereby creating a long-term liability as development proceeds. Alternatively, the cumulative exposure to stressful experiences and concomitant dysregulation of the HPA axis may contribute to ongoing wear and tear on these brain structures. These effects of chronic stress are heightened, given that these areas of the brain have dense concentrations of glucocorticoid receptors, thereby promulgating progressive inefficiency in brain structure and function. For children in low-income environments and those subjected to abuse and neglect, the consequences may be particularly salient for health outcomes across the life span.

ADVERSE PHYSICAL HEALTH OUTCOMES

In addition to cortisol dysregulation, maltreatment appears to be associated with other adverse health outcomes that may be implicated in the development of allostatic overload. For example, maltreatment predicts increased risk for hospital-based treatment of asthma, cardio-respiratory, and infectious disease in childhood (Lanier, Jonson-Reid, Stahlschmidt, Drake, & Constantino, 2010). Early child abuse has been linked to more health-related symptoms (e.g., sleep, eating, general health status), higher body mass index (BMI), lower high density lipoprotein, leptin deficiency, obesity, chronic fatigue syndrome, fibromyalgia, and compromised immune system functioning in childhood and adolescence (Danese et al., 2014; Danese et al., 2011; Danese & Tan, 2014; Heim et al., 2006; Lee, 2010; Miller, Chen, & Parker, 2011; Shirtcliff, Coe, & Pollak, 2009). Furthermore, health liabilities extend into adulthood, as child maltreatment has been found to predict adult cardiovascular disease, elevated inflammation levels, type II diabetes, HIV-risk, self-reported physical symptoms across a range of organ systems, and decreased longevity (Danese et al., 2007; Felitti et al., 1998; Wilson & Widom, 2011). Moreover, child maltreatment has been linked to shortened leucocyte telomere length and it is thought that maltreatment may influence cellular aging (Tyrka et al., 2010).

Miller, Chen, and Parker (2011) proposed a conceptual model to explain why those who experience child maltreatment have an enhanced proinflammatory phenotype. Miller and colleagues (2011) state that stress that occurs during a sensitive developmental period, i.e., when immune function is highly malleable/plastic, becomes embedded in the functioning of the cells that regulate inflammation. Coelho, Viola, Valss-Bass, Brietzke, and Grassi-Oliveria (2014) reviewed 20 studies that examined the association between adults' recollections of child maltreatment and inflammatory markers. Coelho and colleagues (2014) concluded that a history of maltreatment was associated with increased levels of C-reactive protein (CRP), an inflammatory biomarker that is indicative of systemic inflammation. Reichlin (1993) proposed that the neuroendocrine and immune systems interact. Immune responses are thought to alter neural and endocrine function. In turn, neural and endocrine activity are seen as modifying the function of the immune system. The dysregulation of the HPA axis in maltreated persons, who manifest pituitary hyporesponsiveness to corticotropic releasing hormone (CRH) or increased glucocorticoid sensitivity to cortisol, has the potential to bring about a systemic proinflammatory state.

As discussed earlier, a valuable series of studies have examined diverse, long-term health outcomes in an extensive sample of HMO members who were exposed to varying adverse childhood experiences (ACE; Felitti et al., 1998). The ACE factors that were examined included exposure to childhood emotional, physical, and sexual abuse, substance abuse in the family, parental mental illness, domestic violence, and adult criminal behavior. The accumulation of adverse experiences across these risk domains was determined and linked to a range of adult health outcomes. For example, a gradient of exposure to

increasing numbers of ACE factors was associated with a cumulative index of health risk behaviors linked with adult disease and mortality, (i.e., smoking, alcoholism, drug abuse, suicide attempts, high number of sex partners, sexually transmitted diseases, inactivity, obesity). Moreover, a dose–response relationship between ACE exposures and leading causes of death, including heart disease, cancer, chronic bronchitis or emphysema, hepatitis, skeletal fractures, and poor self-rated health, was also observed. Furthermore, ACE factors have been associated with hospitalization for diagnosed autoimmune diseases decades into adulthood and graded relationships between ACE factors and prescription rates for psychotropic medications have been found. This latter finding further illustrates the high rate of serious adult psychiatric morbidity that ensues among children exposed to high levels of adversity.

Cicchetti, Handley, and Rogosch (2015) conducted a study examining child maltreatment, inflammation, and internalizing symptoms. In this multilevel investigation, Cicchetti and colleagues (2015) explored the roles of C-reactive protein, gene variation, and neuroendocrine regulation. The goal of the study was threefold: (1) Determine whether the effect of the timing of child maltreatment on C-reactive protein (CRP), an inflammatory marker, varies by CRP gene variation; (2) explore whether links between salivary CRP and childhood internalizing symptoms depend on the presence and timing of maltreatment experiences; and (3) investigate the role of CRP in the relations between child neuroendocrine regulation and internalizing symptoms and examine whether these associations are moderated by the presence and timing of child maltreatment.

Results indicated that among children with recent onset maltreatment, those with at least one A allele from CRP SNP rs1417938 evidenced significantly higher CRP levels compared with recently maltreated children carrying the TT genotype. Moreover, higher levels of CRP were associated with higher levels of internalizing symptoms only for recently maltreated children. Finally, Cicchetti et al. (2015) did not find support for salivary CRP as a mechanism in the relation between neuroendocrine regulation and childhood internalizing symptoms. These findings highlight the importance of the timing of child maltreatment and have important implications for characterizing variability in inflammation and internalizing symptoms among youth.

Consistent with the concept of AL, Rogosch, Dackis, and Cicchetti (2011) conducted a multidomain assessment of stress-sensitive systems among low-income maltreated and nonmaltreated comparison children. An AL composite was created from measurements of salivary cortisol and dehydroepiandrosterone (DHEA), BMI, waist-hip ratio, and blood pressure. Results indicated that maltreatment and AL independently predicted psychopathology and health difficulties (i.e., parent report of child's physical health status and utilization of health care system). As AL increased, the level of child health and psychological problems increased for all low-income children. Child maltreatment had an additive effect, contributing to the degree of physical and mental health problems beyond that accounted for by the AL composite. Therefore, children with both high AL and a history of maltreatment had the most health problems.

The findings of this investigation have important implications for programs designed to promote physical and mental health in the lives of low-income and maltreated children. Heckman (2006) emphasized the economic and humanitarian value to society of reducing the impact of adverse early family environments on developing children to ameliorate the diminished cognitive capacities ensuring from deprivation and high stress. AL is likely a major influence on these unrealized potentials, through the negative sequelae of stress occurring in early sensitive periods of brain development and progressive accumulation of liabilities that extend to other stress-sensitive systems. Although broad-based efforts to reduce the impact of poverty are crucial, targeted interventions to advance cognitive functioning and self-regulatory capacities (Blair & Diamond, 2008) are vital for enhancing self-righting processes and promoting resilience. For the most vulnerable children in low-SES environments, concerted efforts to prevent the occurrence of child abuse and neglect are of fundamental importance. Early intensive interventions in child maltreatment to establish more sensitive and nurturant parenting, secure attachment, and neurobiological reorganization in maltreated youngsters (Cicchetti, Rogosch, & Toth, 2006; Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011) hold great promise for instilling adaptive developmental trajectories. Consolidated, multisystemic approaches beginning early in development are necessary to reduce environmental stress exposure, child maltreatment, and allostatic overload to improve physical and mental health across the life span.

MALTREATMENT EXPERIENCES AND NEUROBIOLOGICAL DEVELOPMENT

Abnormal brain development is a dynamic, self-organizing process. The perturbations that occur during abnormal brain development can potentiate a cascade of maturational and structural changes that eventuate in the

neural system proceeding along a trajectory that deviates from that generally taken in normal neurobiological development (Cicchetti, 2002b; Cicchetti & Tucker, 1994; Courchesne, Chisum, & Townsend, 1994). For example, early maltreatment, either physical or emotional, may condition young neural networks to produce cascading effects through later development, possibly constraining the child's flexibility to adapt to new challenging situations with new strategies rather than with old conceptual and behavioral prototypes. Thus, early psychological trauma may eventuate not only in emotional sensitization, but also in pathological sensitization of neurophysiological reactivity.

Children who are endowed with normal brains may encounter a number of experiences (e.g., poverty, community violence, child maltreatment) that exert a negative impact on developing brain structure, function, and organization and contribute to distorting these children's experiences of the world (Hackman, Farah, & Meaney, 2010). This provides a unique opportunity for comprehending how environmental factors can bring about individual differences in neurobiological development.

Children may be especially vulnerable to the effects of pathological experiences during periods of rapid creation or modification of neuronal connections. Pathological experience may become part of a vicious cycle, as the pathology induced in brain structure may distort the child's experience, with subsequent alterations in cognition or social interactions, thereby causing additional pathological experience and added brain pathology (Cicchetti & Tucker, 1994). Because experience-expectant and experience-dependent processes may continue to operate during psychopathological states, children who incorporate pathological experience may add neuropathological connections into their developing brains instead of functional neuronal connections (Black, Jones, Nelson, & Greenough, 1998).

As has been stated, child maltreatment affects both neurobiological and psychological processes. Physiological and behavioral responses to maltreatment are interrelated and contribute to children's making choices and responding to experiences in ways that typically produce pathological development. Because maltreated children experience the extremes of caretaking casualty (Sameroff & Chandler, 1975), they provide one of the clearest opportunities for scientists to discover the multiple ways in which social and psychological stressors can affect biological systems. Numerous interconnected neurobiological systems are affected by the various stressors associated with child abuse and neglect (DeBellis, 2001, 2005). Moreover, each of these neurobiological systems influences and is influenced by multiple domains of biological and psychological development. Furthermore, in keeping with the principle of multifinality, the neurobiological development of maltreated children is not affected in the same way in all individuals. Of note, not all maltreated children exhibit anomalies in their brain structure or functioning and identifying protective mechanisms in these children emerges as an important area of future research.

NEUROIMAGING AND CHILD MALTREATMENT

There has been a burgeoning of interest in comprehending how early adverse experiences, such as child maltreatment, exert their effects on the developing brain (Lupien, McEwen, Gunnar, & Heim, 2009). Multiple brain regions and neural circuits are disrupted by the experience of child abuse and neglect. The aberrant neuronal circuitry most likely contributes to the multifinal phenotype observed in maltreated individuals. Magnetic resonance imaging (MRI) technology provides a noninvasive and safe methodology for examining brain morphology, physiology, and function in individuals who have been maltreated. Over the past several decades, neuroimaging investigations increasingly have been conducted with maltreated children and adolescents. Herein, we provide a selective review of these studies.

DeBellis, Keshavan, and colleagues (1999) reported the results of an in-depth whole-brain volumetric analysis of a group of hospitalized maltreated children and adolescents with PTSD and a group of medically and psychiatrically well nonmaltreated comparison subjects. In contrast to findings reported in studies of adults who retrospectively reported their histories of child maltreatment, DeBellis et al. (1999) did not find a reduction in hippocampal volume in the group of maltreated children and adolescents with maltreatment and PTSD. The discrepant findings between the child and adult studies on the effects that maltreatment exerts on hippocampal volume may be a function of the increase in volume that normatively occurs in neurobiological development during adolescence (Spear, 2000). During adolescence, subcortical gray matter structures that include the hippocampus continue to develop, and these normative processes of adolescent brain development may mask any effects that maltreatment and PTSD may exert on the developing limbic system. Alternatively, because the maltreated children with PTSD who comprised the DeBellis et al. (2001) sample were involved in ongoing individual or group treatment, these

psychotherapeutic interventions may have contributed to an increase in hippocampal neurogenesis, thereby eliminating any actual difference between hippocampal volume in maltreated and nonmaltreated individuals.

After controlling for intracranial volume and SES, DeBellis and colleagues (DeBellis, Keshavan, et al., 1999) discovered a number of additional MRI-based brain structural anomalies in their sample of maltreated children and adolescents with PTSD. These included smaller intracranial volumes, cerebral volumes, and midsagittal corpus callosum areas and larger lateral ventricles than in the group of nonmaltreated comparison children and adolescents. DeBellis, Keshavan, et al. also found a positive correlation between intracranial volumes and age of onset of PTSD trauma as well as a negative correlation with the duration of maltreatment that led to a PTSD diagnosis, suggesting that there may be sensitive periods and dose effects for stress-related alterations in brain development. Furthermore, according to DeBellis, Keshavan, et al. their finding that enlarged lateral ventricles in maltreated children and adolescents were correlated positively with the duration of the maltreatment experienced suggested that there may have been neuronal loss associated with severe stress.

In another investigation, DeBellis, Keshavan, Spencer, and Hall (2000) used magnetic resonance spectroscopy (MRS), a safe and novel neuroimaging methodology, to investigate the in-vivo neurochemistry of neurobiological alterations in children's brains. DeBellis and colleagues measured the relative concentration of N-acetyl aspartate (NAA) and creatine in the anterior cingulate cortex of a small group (n = 11) of maltreated children and adolescents who also had PTSD and a healthy nonmaltreated comparison group (n = 11) matched on SES. NAA is considered to be a marker of neural integrity; moreover, decreased concentrations of NAA are associated with increased metabolism and loss of neurons. DeBellis et al. found that maltreated children and adolescents with PTSD had lower NAA-to-creatine ratios, which are suggestive of neuronal loss in the anterior cingulate region of the medial prefrontal cortex, than did the nonmaltreated, SES-matched comparisons. The reduction in the ratio of NAA to creatine buttresses the hypothesis that maltreatment in childhood may alter the development of cortical neurons.

Approximately a dozen studies have replicated the results of DeBellis et al. (1999) that maltreated children and adolescents with PTSD do not have lower hippocampal volume than nonmaltreated comparisons (McCrory, DeBrito, & Viding, 2010). Thus, it appears that the hippocampal reduction effect may be specific to adults with a history of maltreatment (Teicher, Anderson, & Polcari, 2012). Perhaps the stress-induced prolonged exposure to glucocorticoids had a neurotoxic effect and contributed to a reduction in the complexity of hippocampal cells and even to cell death (Lupien et al., 2009). Preclinical research suggests that repeated exposure to stress hormones during development negatively affects neuronal migration, myelination, and neurogenesis, resulting in reduced dendritic spines, gray matter, and white matter connectivity in affected brain regions (Dackis, Rogosch, Oshri, & Cicchetti, 2012; Dannlowski et al., 2012). Therefore, child maltreatment may lead to neurotoxic effects within limbic regions during sensitive periods of development.

Teicher and colleagues (2004) investigated the corpus callosum in children who had been abused or neglected to ascertain whether there were structural abnormalities in its regional anatomy. The corpus callosum connects the left and right hemispheres and is the major myelinated tract in the brain. Regional corpus callosum area was measured by MRI in three groups of children: abused and neglected children, children admitted for psychiatric evaluation, and healthy comparisons. Teicher et al. found that the total area of the corpus callosum of the children who had experienced abuse and neglect was smaller than that of the children evaluated for psychiatric problems and the healthy comparisons. The latter two groups of children did not differ from each other. Child neglect was associated with a 15% to 18% reduction in corpus callosum regions; in contrast, reduced corpus callosum size in girls was most strongly associated with sexual abuse. These findings are congruent with the earlier assertion that negative early experiences can adversely affect neurobiological development.

With respect to corpus callosum and cerebellar volume, there is sound evidence for reduced volume in individuals who have experienced adversity (McCrory et al., 2010). On the other hand, structural MRI results are less consistent for the prefrontal cortex (PFC). It is unclear why there are inconsistent results for volumetric studies of the PFC. Among the possibilities are age differences across studies, variation in maltreatment subtype experienced (e.g., sexual abuse vs. witnessing domestic violence), and methodological differences in scoring MRI scans (e.g., manual tracing, which characterized early studies, vs. automated techniques such as voxel-based morphometry).

Structural neuroimaging studies also provide evidence for deficits in brain volume and in gray and white matter in several regions of the brain. The most prominently affected

appear to be the anterior cingulate cortex, the dorsolateral, orbitofrontal, and ventromedial prefrontal cortex and the hippocampus, amygdala, and corpus callosum (Hart & Rubia, 2012). Diffusion tensor imaging (DTI) studies have revealed deficits in structural connectivity between these areas, thereby suggesting abnormalities in neural networks.

In comparison to the number of studies that have examined structural neurobiological differences in maltreated children, adolescents, and adults, fewer studies have investigated brain functional differences between maltreated and nonmaltreated individuals. Moreover, a very small percentage of these functional studies have been conducted with children. In terms of functional MRI (fMRI), investigations suggest that maltreatment experiences are associated with hypoactivity in the PFC of the dorsofrontal and ventromedial prefrontal cortex. The atypical activation in these brain regions occurs during response inhibition, working memory, and emotion processing tasks (Hart & Rubia, 2012). Relatedly, a neurocognitive study of 3–9-year-old maltreated and nonmaltreated children revealed that the experience of maltreatment during infancy and a chronic history of maltreatment were associated with poorer working memory and inhibitory control performance than children without a history of maltreatment (Cowell, Cicchetti, Rogosch, & Toth, 2015).

Most fMRI studies of maltreated individuals have been conducted during emotion processing tasks (see, e.g., Dannlowski et al., 2013; Grant, Cannistraci, Hollon, Gore, & Shelton, 2011; van Harmelen, et al., 2012; McCrory et al., 2013). The most prominent functional deficits associated with early child maltreatment are in the fronto-limbic brain areas and neural networks that mediate behavioral and affect control (Hart & Rubia, 2012). These investigations have predominately examined amygdala reactivity to various emotion stimuli in maltreated and nonmaltreated adolescents and adults. Herringa, et al. (2013) examined the association of maltreatment experiences during childhood, resting state functional brain connectivity of the amygdala and the hippocampus, and internalizing symptoms. Thus, maltreatment in adolescence may alter the regulating capacity of the fear circuit of the brain leading to increased internalizing symptoms.

Although our discussion of the sequelae of child maltreatment elucidates numerous negative outcomes, it is important to recognize that not all maltreated children are affected similarly and not all succumb to the adverse outcomes accompanying maltreatment. Within developmental psychopathology, the identification of resilience in the context of extreme adversity also has received considerable attention.

CHILD MALTREATMENT AND RESILIENCE

Deviations from the average expectable environment potentiate some individuals toward the development of maladaptive functioning, whereas others demonstrate positive adaptation in the face of the same challenges (Cicchetti, 2010; Masten, 2001). Resilience is conceived as a dynamic developmental process encompassing the attainment of positive adaptation despite exposure to significant threat, severe adversity, or trauma that typically constitute major assaults on the processes underlying biological and psychological development (Cicchetti, 2010; Luthar, Cicchetti, & Becker, 2000). Resilience is not a magical phenomenon (Masten, 2001). The same developmental cascades which can amplify maladaptive outcomes over time can perpetuate or amplify positive outcomes when the individual benefits from some combination of experiences and/or biological propensities that tip the initial balance towards adaptive outcomes (Cicchetti, 2013).

The occurrence of resilient outcomes in approximately 10%–25% of maltreated children point out that self-righting tendencies in human development may be strong, even in the face of deviance and failure in the environment (Cicchetti, 2013; Sameroff, 1983). At one level, different parts of the brain may attempt to compensate, and at another, maltreated individuals may seek out new experiences in areas where they possess strengths. Because plasticity is a central feature of the mammalian brain, early neurobiological anomalies or aberrant experience should not be considered as determining the ultimate fate of the maltreated child (Cicchetti & Curtis, 2006). Discovering how maltreated children develop and function resiliently despite their multitude of adverse experiences offers promise for informing the design, implementation, and multilevel evaluation of prevention and intervention programs (Luthar & Cicchetti, 2000).

Research on the correlates, pathways, and developmental course of resilient functioning in maltreated children has predominantly been gleaned from investigations that have focused on psychosocial variables (see Cicchetti, 2013 for a review). For example, in a 3-year longitudinal study conducted in a summer camp context, Cicchetti and Rogosch (1997) found that ego-resiliency and moderate ego-control, as well as self-system variables, predicted resilient functioning in maltreated children; in contrast, ego-resiliency, perceived emotional availability of the

mother, and relationship quality with camp counselors were significantly more likely to be predictive of resilient functioning in nonmaltreated children from comparable low-SES backgrounds. Relationships were more critical to developing resilient outcomes in nonmaltreated children, whereas self-system processes and personality characteristics were more central to resilient outcomes in maltreated children. Thus, self-reliance, personal conviction, and self-confidence, in concert with interpersonal reserve, may bode well for the development of resilient adaptation in maltreated children.

In 2003, Curtis and Cicchetti urged researchers to incorporate neurobiological and molecular genetic assessments into their measurement batteries aimed at discovering pathways to resilient functioning. Technological advances in neuroscience and molecular genetics have helped to pave the way for an unprecedented opportunity to examine resilience from a multiple levels of analysis perspective. To date, few multilevel studies of resilient functioning in maltreated children have been completed. As investigations of biological contributions to resilience only have been conducted recently, each of these studies has been cross sectional in nature.

Curtis and Cicchetti (2007) sought to discover whether the positive emotionality and increased emotion regulatory ability associated with resilient functioning would be related to greater left frontal EEG activity. A large body of literature concerning the meaning and correlates of hemispheric asymmetries in EEG activity has suggested that this ubiquitous phenomenon indexes a neural system that has emotion-specific influences whereby the two hemispheres of the cerebral cortex have been found to be differentially involved in emotion (Davidson, 2000). Specifically, the left hemisphere is associated with positive emotions/approach behavior and the right hemisphere is linked with negative emotions/withdrawal behavior. Emotions, and in particular, positive emotion and good emotion regulatory abilities, have consistently been associated with resilient adaptation. For example, Bonanno et al. (2007) coded genuine (Duchenne) smiling and laugher and non-Duchenne smiling from videotapes of older adolescent and young adult females. Approximately half of the women had experienced sexual abuse during their childhoods. Bonanno and colleagues found that women who displayed genuine positive affect were significantly more likely to have better social adjustment two years later. In contrast, sexually abused women who expressed positive emotion in the context of describing a prior childhood sexual abuse experience had poorer long-term social adjustment, whereas those who exhibited positive affect when describing nonabuse experience had improved social adjustment. Thus, the potential connection of hemispheric EEG asymmetry with resilience lies in their common linkages with emotion and emotion regulation.

EEG asymmetry across central cortical regions distinguished between children with high and low resilient functioning such that left hemisphere activity characterized those maltreated children, who were adapting resiliently based on a competence composite index (e.g., good peer relations, adapting successfully to school, low levels of depressive symptomatology, low externalizing and internalizing psychopathology). Moreover, a behavioral measure of emotion regulation based on 35 hours of observation of the children, also independently contributed to the prediction of resilience in maltreated and nonmaltreated children.

The investigation of a neural-level phenomenon such as hemispheric EEG asymmetry, in the context of resilient adaptation underscores that there is certainly no one single characteristic that will be ascendant in the process of resilience over the course of development. Resilience is a dynamic, interactive, and bidirectional process between multiple levels across time, none of which holds primary importance at any given moment. However, the relative importance of various biological and psychological processes, although inevitably interrelated, may also vary across development.

In another multilevel investigation, resilient functioning in maltreated and nonmaltreated low-income children in relation to the regulation of two stress-responsive adrenal steroid hormones, cortisol, and dehydroepiandrosterone (DHEA), as well as the personality constructs of ego resiliency and ego control, was examined. The steroid hormones chosen as potential predictors of resilience were the two primary adrenocortical products of secretory activity of the hypothalamic-pituitary-adrenal (HPA) axis. The capacity of individuals to elevate cortisol levels in response to exposure to acute trauma is important for survival. DHEA exerts an impact upon a diverse array of biological actions, including effects on the immune, cardiovascular, endocrine, metabolic, and central nervous systems.

A composite measure of resilience was utilized that included multimethod, multi-informant assessments of competent peer relations, school success, and low levels of internalizing and externalizing symptomatology. Cicchetti and Rogosch (2007) found that personality characteristics, ego resiliency and moderate ego overcontrol and the adrenal steroid hormones associated with stress (i.e., cortisol and DHEA) made independent and noninteractive contributions to resilience. Although operating at different

levels of analysis, behavioral/psychological and biological factors each made unique contributions to resilience.

Cicchetti and Rogosch (2007) found that higher morning levels of cortisol were related to lower levels of resilient functioning for the nonmaltreated children. High basal cortisol may indicate that nonmaltreated children are experiencing greater stress exposure and, consequently, are constrained in their ability to adapt competently. Within the group of maltreated children, differences in cortisol regulation were found as a function of the subtypes of maltreatment experienced. Physically abused children with high morning cortisol had significantly higher resilient functioning than physically abused children with lower levels of morning cortisol. The positive role of increased cortisol for physically abused children is divergent from the more general pattern of higher cortisol being related to lower resilient functioning that was discovered in the nonmaltreated and sexually abused children in this study.

Prior research on neuroendocrine regulation has indicated that physically abused children generally exhibit lower levels of morning cortisol secretion (Cicchetti & Rogosch, 2001b), especially children who experienced physical abuse early in life (Cicchetti et al., 2010; Cicchetti et al., 2011). It may be that the subgroup of physically abused children who were able to elevate cortisol to cope with stressful vicissitudes in their lives were demonstrating a greater striving for resilient adaptation. In contrast, the larger subgroup of physically abused children with lower levels of morning cortisol may have developed hypocortisolism over time in response to chronic stress exposure. As a result, for these children there may be a diminished capacity to mobilize the HPA axis to promote positive adaptation under conditions of ongoing stress. In addition, Cicchetti and Rogosch (2007) found that the very low level of resilience among sexually abused children with high basal cortisol may be a product of their different traumatic experiences and consequences of chronic excessive vigilance and preoccupation, with commensurate HPA axis hyperarousal.

Finally, maltreated children with high resilient functioning exhibited a unique atypical pattern of a relative DHEA diurnal increase. Maltreated children who have the capacity to elevate DHEA over the course of the day may be better equipped to cope with the demands of high chronic exposure to stress and to adapt competently. In contrast, the nonmaltreated children who functioned resiliently did not exhibit the pattern of diurnal DHEA increase; instead they displayed the lowest levels of DHEA across the day. DHEA has been shown to generate effects that are associated with resilience. For example, DHEA counteracts the harmful effects of hypercortisolism, thereby potentially conferring neuro-protection on the brain (Charney, 2004).

The GxE studies on psychopathology reviewed earlier in this chapter are instructive and relevant for research on resilient functioning because they provide an illustration of how genetic variation may confer protection against mental disorder on individuals who have experienced child maltreatment. However, in our view, the absence of mental disorder is conceptually distinct from resilience, a dynamic multidimensional developmental process indicated by positive adjustment across domains of competent functioning despite the experience of significant adversity. Moreover, the presence of mental disorder does not preclude the achievement of resilient functioning. Many persons with mental disorder not only experience periods of remission, but also an appreciable number manage to function in an adaptive fashion for prolonged periods of their lives (Hinshaw & Cicchetti, 2000).

To our knowledge, there has been only one molecular genetic investigation that has specifically set out to test the hypothesis that particular genetic variants might be related to resilient functioning in the presence of child maltreatment. To examine the processes underlying the development of resilience at the molecular genetic level of analysis, Cicchetti and Rogosch (2012) embarked on research aimed at discovering whether there were genetic elements, in interaction with the experience of child maltreatment, that were associated with higher levels of resilient functioning in maltreated and nonmaltreated school-aged children. A multicomponent index of resilient functioning was identified. Four theoretically and empirically informed genes that have been found to be related to behaviors known to be associated with resilient functioning, 5-HTTLPR, CRHR1, DRD4—521C/T, and OXTR, were chosen and genetic variants in each of these genes were investigated.

Maltreatment consistently exerted a strong, adverse main effect on resilient functioning; however, none of the gene variants of the four respective genes were shown to have a main effect on resilience. In contrast, GxE effects were obtained and a similar pattern emerged for all four genes—a particular genotype was found to differentiate between the level of resilient functioning in maltreated and nonmaltreated children more strongly. Contrary to the typical GxE studies on psychopathology, the results of the Cicchetti and Rogosch (2012) investigation revealed that genetic variation had a negligible effect for the maltreated group in predicting resilient functioning. In contrast, genotype was shown to contribute to higher resilient functioning in nonmaltreated children when they possessed

a particular genotype, at least relative to the maltreated children with the same genotype.

In the case of 5-HTTLPR, nonmaltreated children with the SS genotypic variant were significantly more likely to have higher resilient functioning, whereas maltreated children who possessed the same genetic variant had significantly lower resilient functioning. These findings are consistent with a differential susceptibility to environmental influences interpretation (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011). According to this perspective, the characteristics individuals possess that render them disproportionately vulnerable to adverse experiences also make these same individuals disproportionately likely to profit from supportive contexts. For children who possess the same s/s genotypic variant of 5-HTTLPR, nonmaltreated children, in the context of a more normal childrearing environment, achieved higher resilient functioning, whereas maltreated children, in the context of an adverse childrearing environment, demonstrated lower resilient functioning (cf. van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012).

For CRHR1, nonmaltreated children with zero copies of the TAT haplotype had significantly higher levels of resilient functioning relative to maltreated children with the same number of copies of the TAT haplotype. Once again, these findings are consistent with a differential susceptibility to the environment perspective (Belsky & Pluess, 2009; Ellis et al., 2011). Maltreated and nonmaltreated children had the same genetic variant (i.e., zero copies of the TAT haplotype); however, the nonmaltreated children showed higher levels of resilient functioning, whereas the maltreated children (living in a more stressful context) evinced lower levels of resilient functioning.

Analyses of the DRD4 (dopamine receptor) -521C/T single nucleotide polymorphism (SNP), revealed that nonmaltreated children and, in particular, those with the TT genotype, were more likely to exhibit significantly higher resilient functioning scores than were maltreated children with this same genotype. The maltreated children manifested significantly lower levels of resilient functioning. As with the previous results for 5-HTTLPR and CRHR1, findings with DRD4 -521C/T provide support for the differential susceptibility to environmental influences perspective.

In further analyses, Cicchetti and Rogosch (2012) examined the relation between number of maltreatment subtypes and DRD4 -521C/T genotype to resilient strivings. Maltreated children who had experienced three or four subtypes fared dramatically worse with the TT genotype, whereas nonmaltreated children with this genotype fared the best. Maltreated children with 3–4 subtypes of maltreatment with the CC or CT genotypes were indistinguishable in level of resilient functioning from nonmaltreated children with these genotypes. Despite the very large detrimental effect that extensive maltreatment exerts on resilient functioning independent of genotype, these results exemplify how the three to four maltreatment subtype groups exhibit the same level of resilient functioning as do nonmaltreated comparisons with the same CC or CT genotypes.

Finally, with OXTR (oxytocin receptor), not being maltreated was related to significantly higher resilient functioning scores; in contrast, maltreatment was strongly related to lower levels of resilient functioning. In particular, nonmaltreated children who had either the AA or AG genotypes of OXTR displayed greater levels of resilient functioning than maltreated children with these same genotypes. Consistent with the findings obtained with the three previous candidate genes, the results provide strong support for the differential susceptibility to environmental influences framework.

It is noteworthy that Cicchetti and Rogosch (2012) identified different gene variants as differentially important through contrasting maltreated and nonmaltreated children and their level of resilient functioning (i.e., low, medium, high). The variation among the genotypes and their relation to functioning differences would not be apparent without the consideration of experience. The genes did not have a singular role, outside of experiential context. The contrast between groups of maltreated and nonmaltreated children was therefore important for understanding development in normal and atypical rearing environments.

Cicchetti and Rogosch's (2012) findings suggest that the genes included in this investigation appear to be minimally related to resilient functioning in maltreated children. Maltreatment consistently had a statistically significant main effect on resilient functioning for each of the genes examined. Genetic variation had more of an impact on resilient functioning among the nonmaltreated children who also resided in stressful poverty-laden environments. Accordingly, it appears that the powerful maltreatment main effects may have overshadowed any potential contribution of genetics to resilient functioning in abused and neglected children. Despite the multidomain assessment of adaptive functioning and the large well-defined sample of maltreated and nonmaltreated children, a limitation of the study is its cross sectional nature. Because resilience is a dynamic developmental construct that is not immutable, future investigations of gene-environment

interaction and resilient functioning should be prospective and longitudinal.

Although many investigations of child maltreatment include racially and ethnically diverse populations, possible differences associated with these demographic characteristics are not consistently discussed. Thus, we next turn our attention to this important demographic variable.

RACE AND ETHNICITY

In part as a function of concerns about the overrepresentation of children of color in the child welfare system and heightened awareness about disparities in access to quality health and mental health services for ethnic minorities, examinations of child maltreatment have increasingly sought to incorporate an understanding of issues related to race and ethnicity. The importance of this movement is underscored by findings from the most recent National Incidence Study. As stated earlier, NIS-4, the first NIS to detect racial and ethnic differences in rates of child maltreatment in the United States (Sedlak et al., 2010), found that Black children experience maltreatment at higher rates than do White children in several subtypes of maltreatment, including higher rates of physical abuse, overall abuse and overall maltreatment according to both the Harm and the Endangerment Standard. Under the Endangerment Standard, Black children also had higher rates of emotional neglect and overall neglect. The authors of the report qualified these findings by noting that NIS-4 estimates were more precise than those contained in prior NIS reports. Importantly, they also highlighted the role of socioeconomic status in these findings, noting widening income gaps between Black and White families, with children in Black families being more likely to reside in low-income families.

A growing body of literature has examined factors such as ethnic differences in the disclosure of abuse (Meston, Heiman, Trapnell, & Carlin, 1999), utilization of varied definitions of abuse (Collier, McClure, Collier, Otto, & Polloi, 1999), and differences between what constitutes culturally sanctioned parenting and abusive parenting (Miller & Cross, 2006). However, despite recognition of the importance of better understanding maltreatment in the context of racial and cultural milieus, research in child maltreatment to date has done little to clarify these issues (Elliott & Urquiza, 2006). Unfortunately, progress on research in this area has been hindered by confounds between race and ethnicity, considerations related to low socioeconomic status among minorities, reliance on retrospective reports of maltreatment, and the utilization of small and geographically diverse samples. Thus, with the exception of robust differences in parenting styles identified among diverse ethnic and racial groups, research on race, ethnicity, and child maltreatment has yielded conflicting results (Elliott & Urquiza, 2006; Sedlak et al., 2010).

Much less of the extant child maltreatment literature has examined differential effects of maltreatment as a function of racial and ethnic backgrounds. Current theoretical perspectives differ with respect to predictions about the consequences of maltreatment for children of different races and ethnicties. The racial invariance hypothesis maintains that the effect of social influences on outcomes should be similar, regardless of race or ethnicity, if there is equal exposure to the environmental event (Sampson & Bean, 2006). In accord with this perspective, the sequelae of child maltreatment should not be expected to differ as a consequence of race/ethnicity. Conversely, another perspective maintains that effects of maltreatment may be magnified for children from minority groups due to their exposure to racism and other forms of violence (Wyatt, 1990). Finally, it is possible that the effects of maltreatment may be less severe for members of racial/ethnic minorities because children from these backgrounds may have developed resilience as a function of coping with higher levels of stress. Although an appealing perspective, the low rates of resilience typically found in maltreated children argue against this possibility.

While some studies have identified racial differences in individuals with histories of maltreatment with respect to increased arrests for violent crimes (Maxfield & Widom, 1996), posttraumatic stress symptoms (Canez 2000; Roberts, Gilman, Breslau, & Koenen, 2011), and alcohol problems in adulthood (Caetano, Field, & Scott, 2003), others have failed to identify differences (Hatcher, Maschi, Morgen, & Toldson, 2009; Lau, Litrownik, Newton, Black, & Everson, 2006). In efforts to shed further light on this issue, multiple domains of functioning were examined in adults with documented histories of neglect during childhood (Widom, Czaja, Wilson, Allwood, & Chauhan, 2013). The findings of this investigation yielded support for each of the theoretical perspectives previously described. Thus, rather than providing clarification on the relation between maltreatment and outcomes, these findings highlight the complexity of this area of investigation as numerous other factors such as racism and differences in acceptance of mental health services may have contributed to the findings on outcomes in adulthood.

Although inconsistency exists with respect to racial/ethnic differences in child maltreatment, clear differences

emerge with respect to case status in the child welfare system (Hill, 2007). Black and Latino children are more likely to be removed from their homes, to remain in foster care longer, to have more placement changes once removed from their homes, and to be less likely to be reunified with their parents once removed (Hill, 2007). Thus, the criticality of continuing to understand the role of ethnic and racial factors in relation to child maltreatment and the importance of incorporating these variables into future research cannot be minimized. Similarly, considerations associated with gender also warrant attention.

Now that we have concluded our discussion of the consequences of child maltreatment, it is important to consider methodological issues that may affect the strength of conclusions to be drawn from this body of work.

METHODOLOGICAL ISSUES IN MALTREATMENT RESEARCH

Despite advances that have occurred with respect to the sophistication of empirical research in the area of child maltreatment, a number of difficult methodological issues require further attention. As evident from our discussion of the sequelae of child maltreatment, research in maltreatment is complex for a number of reasons, which we elaborate below.

Definitional Considerations

As discussed earlier it is critical that agreement on definitions of child maltreatment occurs. Despite the fact that progress has been made in terms of increased rigor in definitions of child maltreatment, investigators continue to vary in their approaches to definition. Results across studies are likely to diverge considerably if single subtypes of maltreatment are examined rather than addressing the high prevalence of multiply occurring subtypes. Issues related to perpetrator, severity, chronicity, and developmental period during which maltreatment occurs also should be considered. However, limitations related to sample size, difficulty accessing comprehensive information due to legal restrictions on access to maltreatment registries, and report biases in parents and children often impede such efforts. Although the conduct of statistical analyses for all such variables may not be possible, ideally investigators should present descriptive information on these issues. In addition, clear information needs to be provided on how the maltreatment experience, including decisions on the assignment of subtype, was determined. Moreover, sequelae associated with particular subtypes that may not be immediately apparent but that may emerge over time highlight the importance of conducting longitudinal investigations.

Multiple Subtypes

It is clear that it is rare that a child who has been maltreated experiences a single subtype of maltreatment. When multiple subtypes occur, it is challenging to determine how best to categorize the maltreatment experience. One strategy that has been used involves basing the main subtype designation for analytic purposes on the most societally egregious form of maltreatment, with categorization of sexual abuse, physical abuse, neglect, and emotional maltreatment ranging from most to least severe. In this methodological approach, if a child had been both physically abused and neglected, then they would be categorized as physically abused. Another approach suggests that assignment of the main subtype of maltreatment be based on the most severe form of maltreatment experienced. Thus, if a low level of physical abuse occurred, but a very severe neglect experience were present then the child would be classified as neglected. Regardless of the method adopted, it is critical that investigators clearly describe how the assignment to maltreatment group was made.

Comorbidity

Although concerns around the presence of comorbid disorders are a challenge for psychopathology research in general, this is a particularly problematic issue when investigating the sequelae of child maltreatment. Research consistently demonstrates that maltreatment is highly associated with other negative outcomes, including depression, PTSD, antisocial behavior, and substance use/abuse. When present, therefore, it becomes difficult to ascertain if a given negative outcome is directly attributable to maltreatment or to the co-occurring psychopathology. This is particularly challenging because it is usually impossible to ascertain which condition preceded the other. Again, although it may not be possible to categorize and analyze participants by the presence or absence of co-occurring psychopathology, when possible descriptive information on the presence of psychopathology should be provided.

Economic Adversity

Much of the extant research on child maltreatment has been conducted with economically disadvantaged samples.

Although maltreatment is not limited to the low-income sector, children who come to the attention of authorities are much more likely to reside in families from the lower socioeconomic strata. Because a myriad of risks accompany residing in poverty, including exposure to community and/or domestic violence, stressors associated with difficulty meeting basic needs, and being a member of a racial or ethnic minority group, it can be particularly challenging to recruit and to retain participants. In fact, no-show rates with this population, even when home visits are schedule, frequently average 50% of scheduled appointments. Moreover, research staff are routinely faced with very difficult situations when they enter high crime communities. Thus, safety concerns need to be addressed. In addition to challenges accessing and retaining research samples, it is difficult to disentangle the effects of maltreatment from the co-occurring risk factors that are present. In efforts to minimize these issues, increased research needs to be conducted with maltreated children from a range of socioeconomic backgrounds.

Prevention and Intervention

Methodological challenges also accompany the conduct of research on prevention and intervention outcome studies. As discussed earlier, recruitment and retention, even for basic research studies, is quite difficult. This becomes even more complex when enrolling maltreating families in intervention trials. Maltreating families are often not seeking treatment and typically may not even acknowledge that there is a problem and that they or their children require assistance. We know that retention in randomized control trials (RCTs) is problematic even in treatment-seeking populations, so it is not surprising that it emerges as a significant issue with nontreatment seeking maltreating families. Once enrolled, further complications arise. When ongoing maltreatment is detected, a report must be filed with Child Protective Services, often resulting in a family becoming angry and withdrawing from treatment. Attrition is further exacerbated if a child is placed in foster care or, when studying children already in foster care, if placement changes occur. Issues related to high housing mobility and too often disconnected or changing cell phone numbers also make the consistent tracking of families difficult. Given the high co-occurrence of domestic violence and child maltreatment, the offending partner may be threatened by the involvement of the child or partner in services and interfere with their participation. All of these variables coalesce to make the attainment of large samples in maltreatment intervention studies particularly challenging. Unfortunately, smaller sample size results in reduced statistical power to detect treatment effects. As the conduct of multilevel investigations of treatment outcome becomes increasingly important, the incorporation of psychophysiological and genetic assessments into research batteries will require even larger samples. Although investigators have developed creative methods of facilitating recruitment and retention of participants, attaining large samples remains difficult. One possible solution is to utilize multiple sites for enrollment. However, the feasibility of this is hampered by the high costs of RCTs in combination with federal funding caps.

In summary, although much progress has occurred since child maltreatment was first identified as a factor that contributes to atypical developmental processes, significant challenges remain that need to be addressed if this area of research is to continue to advance. Moreover, the importance of ensuring the translation of this body of knowledge into clinical and social policy domains has been increasingly recognized.

TRANSLATIONAL RESEARCH

Translational research refers to the examination of how basic behavioral and biological processes can inform the diagnosis, prevention, treatment, and delivery of services for individuals at risk for, or who have developed, a mental illness (National Advisory Mental Health Council on Behavioral Science Workshop, 2000). Consistent with a developmental psychopathology perspective (Cicchetti & Toth, 2006, 2009; Rutter & Sroufe, 2000), translational research can best be viewed as reciprocal in nature, with both basic researchers and individuals involved in the provision of clinical care benefitting from input derived from the other domain. The impetus to conduct translational research in the behavioral sciences emanated largely from the National Institute of Mental Health (Insel, 2005; Insel & Scolnick, 2006) and was spurred by the recognition of the tremendous individual, social, and economic burden associated with mental illness (National Advisory Mental Health Council on Behavioral Sciences, 2000). As discussed earlier, a considerable body of research has examined the effect of child maltreatment on psychological and, increasingly, biological functioning (Cicchetti & Valentino, 2006; McCrory et al., 2010) and this scientific knowledge lends itself to the development, evaluation, and exportation of models of intervention designed to disrupt the cascade of negative developmental processes (Masten & Cicchetti, 2010).

Because the formation of a secure attachment relationship with the primary caregiver is one of the most important and universal tasks during the first year of life, and because child maltreatment has been shown to disrupt the development of secure attachments, the provision of interventions to promote attachment security in maltreated children has emerged as an important area of translational research.

Dozier and colleagues (2008), working with a maltreated foster care population, developed Attachment and Biobehavioral Catch-up (ABC) as an intervention for foster parents. The three main components of this brief attachment theory informed intervention are to 1) provide an environment in which the foster child can feel nurtured and loved even when the parent feels pushed away by the child; 2) help the caregiver work through personal issues that may be interfering with their caregiving abilities; and 3) offer a highly controllable interpersonal environment to allow children to better regulate at the bio-behavioral level (Dozier, 2003; Dozier et al., 2008). The ABC intervention is delivered in 10 joint parent–child sessions, and research supports its efficacy at promoting adaptive child attachment behaviors and regulating cortisol. Children from dyads participating in the ABC intervention displayed fewer avoidant behaviors in attachment system eliciting situations compared with children from dyads who received an educational intervention (Dozier et al., 2009). Additionally, cortisol production in foster infants and toddlers who received the ABC intervention resembled patterns similar to those found in children who had never been in foster care and was different from patterns found in foster infants and toddlers whose caregivers participated in an educational intervention (Dozier et al., 2008).

Moss and colleagues recently demonstrated the efficacy of a very brief (eight, 90-minute sessions) parent–child intervention compared with a control condition to reorganize attachment for maltreated children ages 1 to 5 (Moss et al., 2011). Intervener structured parent–child play sessions were videotaped and then watched immediately with the parent during the session to discuss parental observations and reinforce sensitive parental behavior (Moss et al., 2011). Children in the intervention condition were more likely to change from insecure or disorganized attachments to secure attachments after the 8-week intervention than the children in the control condition.

A widely utilized and evaluated intervention for young children with histories of maltreatment, Child Parent Psychotherapy (CPP; Lieberman & Van Horn, 2005), has its origins in attachment theory, developmental psychopathology, and stress and trauma work, while also being informed by cognitive-behavioral and social learning theories (Lieberman & Van Horn, 2009). In recent years, CPP has gained increased attention as an evidence-based, culturally sensitive treatment for maltreated children and their caregivers.

Rather than focus individually on the child or parent, the therapist's client in CPP is the relationship between the caregiver and child. Through dyadic sessions, the therapist utilizes the child's spontaneous play and naturally occurring interactions between the parent and child as a vehicle for understanding maladaptive relational patterns and as an entryway for therapeutic change. The therapist encourages mutually enjoyable interactions between the parent and child, provides a voice for the child to interpret needs that the parent may be struggling to understand, and encourages developmentally appropriate parental expectations.

An additional focus of CPP involves helping the parent develop insight into how the ghosts from maladaptive relationships in his or her past can be influencing the present day interactions with the child in an effort to break the intergenerational transmission of maladaptive relational representations from parent to child (Fraiberg, Adelson & Shapiro, 1975). The CPP model also recognizes the influence of broader contextual factors on the occurrence of child maltreatment and on the developing relationship between the parent and the child.

CPP has been found to be efficacious in a number of RCTs. Cicchetti and colleagues conducted an RCT of CPP compared with a psychoeducationally based parenting intervention (PPI) for maltreated infants and their primary caregivers (Cicchetti, Rogosch, & Toth, 2006). Preintervention, 87.5% of infants in the CPP condition and 83.3% in the PPI intervention evidenced disorganized attachments. Postintervention, these rates had decreased to 32% and 45% respectively for CPP and PPI, with the majority of toddlers in each intervention developing secure attachments by the end of the intervention. The two intervention groups had higher rates of securely attached children postintervention than the community standard group, although they did not differ from each other. Results provide strong support for the efficacy of CPP in promoting secure attachments in infants from maltreating families.

Another randomized clinical trial, conducted by Toth and colleagues, sought to explore the impact of CPP on preschool children's representations of self and mother (Toth et al., 2002). Children and their caregivers were randomly assigned to CPP, PPI, or community standard, and representational models were assessed with the MacArthur Story-Stem Battery (Bretherton et al., 1990).

Children in the attachment-based intervention, CPP, experienced significant declines in negative self-representations and maladaptive maternal representations and significant increases in positive self-representations and mother-child relationship expectations from pre-to postintervention. While changes in representations were also found in the PPI condition, negative self-representations decreased significantly more in CPP than with PPI, and positive self-representations and mother–child relationship expectations improved nonsignificantly in the CPP relative to the PPI condition. These findings highlight the efficacy of CPP for reworking representations of self and other in maltreated children.

In addition to promoting attachment security in maltreated infants and improving representations of the self in maltreated preschoolers, CPP also promotes positive child adaptation in other domains. CPP was more effective than community-standard-plus –case-management at decreasing child behavioral problems and trauma symptoms for children aged 3 to 5 years who had been exposed to marital violence (Lieberman, Van Horn & Ghosh Ippen, 2005). A 6-month follow-up study of CPP found that reductions in child behavior problems were maintained, suggesting the durability of CPP for treating child symptoms (Lieberman, Ghosh Ippen & Van Horn, 2006). More recently, the sustained efficacy of CPP in promoting secure attachment 1-year posttreatment has been demonstrated (Pickreign Stronach, Toth, Rogosch, & Cicchetti, 2013). Not only did children receiving CPP have higher rates of security than children in the psycho-educational parenting model, but rates of disorganized attachment did not differ between children who received CPP and the nonmaltreated comparison children. Thus, although CPP and a psychoeducational parenting intervention both facilitated the completion of treatment, only CPP resulted in sustained security of attachment, suggesting that, while parenting interventions alone may be effective in the short term, they may not result in sustained attachment security over time.

The previous findings support the efficacy of CPP in controlled research trials; however, it is critical that preventive interventions be exported to the clinical world more broadly once efficacy has been established. CPP was recently examined in a community setting emphasizing wraparound care for diverse youth in foster care (Weiner, Schneider & Lyons, 2009). Child traumatic stress symptoms and behavioral and emotional needs decreased significantly for African American, biracial, and Hispanic children receiving the CPP intervention, but not for White children (Weiner et al., 2009). Additionally, risk behaviors decreased and strengths increased for African American and biracial children participating in this study (Weiner et al., 2009).

The feasibility and effectiveness of CPP was also examined in a community setting with families in which the parents had maltreated their children and were court-ordered to participate or were identified as at high risk for abuse or neglect (Osofsky et al., 2007). Attrition was high, with more than 50% of families dropping out before engagement or during treatment; however, increased behavioral and emotional responsiveness and positive discipline were observed in the caregivers who completed treatment, as was decreased intrusiveness. Additionally, development improved in at least one domain (communication, gross motor, fine motor, problem solving, or personal–social) for 50% of the children receiving CPP who had previously been screened as at risk for developmental delay. Importantly, during the first three years of the pilot study, there were no new reports of child abuse or neglect involving children completing CPP. These studies provide preliminary evidence for the feasibility of utilizing CPP with families willing to engage in a community setting, and results suggest that child symptom reduction and improved parenting are attainable when CPP is exported from the laboratory into the nonacademic clinical arena.

More recently, research has coalesced to suggest that early preventive interventions with maltreated children are capable of promoting normative neurobiological development (Cicchetti et al., 2011; Fisher, Stoolmiller, Gunnar & Burraston, 2007), highlighting the continued importance of studying change processes in the lab while applying efficacious interventions in the community.

A relatively new frontier with respect to evaluating and translating knowledge on efficacious interventions emanates from genetics research. As knowledge on the interplay of genes and the environment has increased, the benefits for prevention efforts have been suggested by both animal and human research. Importantly, as knowledge of genetic moderation with respect to prevention and treatment outcome increases, ethical questions also arise. Some may suggest that more cost-effective and efficient interventions could be delivered if youth with particular genetic constellations that place them at risk for maladaptive outcomes are screened and that only those most likely to benefit from a given intervention subsequently receive it. However, a number of considerations argue against this approach (Howe et al., 2010). First, single genes or single GxE combinations fail to account for sufficient variance in outcomes to support screening for intervention provision. Most likely, multiple developmental pathways will eventuate in positive outcomes, a concept consistent with

multifinality. It is more likely that genes will constrain or enhance various pathways than that whey will deterministically contribute to outcomes, in part because the same genetic pattern may constrain a pathway in one context and enhance the same pathway in another context (Howe et al., 2010). The multiply influenced course of development cautions that genetic screening for selective intervention is unlikely to provide significant benefits in advancing intervention efforts, particularly given the current nascent state of research on GxE and intervention outcomes.

Although basic research is increasingly being translated to the prevention and treatment of child maltreatment, the growth of basic research knowledge has generally surpassed its application to mental disorders more generally. The prevention of and treatment for the sequelae of child maltreatment is not an exception to this unfortunate reality. Perhaps even more disconcerting is the fact that the majority of maltreated children do not present at mental health clinics but rather are in contact with systems such as child welfare, law enforcement, and criminal justice where their trauma histories are typically not identified (Harris, Lieberman, & Marans, 2007). As a result, even when evidence-based treatments are available, maltreated children typically fail to receive them.

To bridge the gap between basic and applied research and its application to problems of clinical importance associated with child maltreatment, investigators and clinicians must stretch beyond traditional boundaries. Collaborations across disciplines are necessary if areas as diverse as neuroscience, genetics, emotion, cognition, social cognition, and interpersonal processes are to be incorporated into addressing the needs of children in maltreating families (Toth, Manly, & Nilsen, 2008). The needed areas of expertise also will necessarily differ depending on the ultimate goals but could include individuals with expertise on various cultural contexts and knowledge of various systems that would be needed to support the translational efforts and community acceptance. As efforts have expanded to incorporate basic research knowledge into clinical arenas, it has become increasingly clear that this is a gradual process. To begin, it is critical that those conducting basic research are committed to conceiving their questions with the goal of having findings ultimately inform applications of the knowledge gained (Cicchetti & Toth, 2006). Clearly, before theoretically informed models of prevention or intervention can be developed, applied to maltreating populations, and evaluated, there must be an understanding of the mechanisms and processes that contribute to a maladaptive course of development. As an exemplar of this process, the extensive basic research conducted on attachment theory and the consequences associated with children developing insecure or disorganized attachments to their primary caregivers contributed to the development of CPP. This theoretically derived intervention was then rigorously tested in multiple efficacy trials to determine its utility for maltreating families and for families with domestic violence in highly controlled research settings. Now that efficacy has been established, effectiveness studies have been and are currently being undertaken to determine the feasibility of exporting this empirically based treatment into the broader clinical arena. As a last step in this process, it is important for the scientific community to be open to feedback from those implementing interventions in the field and to use this information when revising interventions and seeking mediators and moderators of treatment efficacy. As will be discussed below, it also is critical that evidence-based models of intervention continue to be evaluated once exported to new community settings. Such initiatives will increase the probability that research will ultimately result in informing social policy for maltreated children.

An example of the exportation of evidence-based models into community settings with continued evaluation is currently being conducted in Rochester, New York. In 2007 the Monroe County Department of Human Services and the United Way of Greater Rochester funded an initiative to aid the community in making progress towards translating efficacy findings and increasing the availability of prevention services for child maltreatment. Building Healthy Children (BHC) targets young mothers who have had a child before the age of 21 and are living in poverty. Mother–child dyads are referred through Pediatrics Departments at local hospitals. There are numerous risk factors within this population, including: domestic violence, maternal depression, criminal activity, indicated CPS reports as children, and sexual abuse histories.

BHC provides a tiered service pyramid that offers evidence-based interventions according to each family's level of need (Paradis, Sandler, Manly, & Valentine, 2013). Families enrolled in the program begin with a home visit by a pediatric social worker and a paraprofessional outreach worker, during which time the needs of mother and child are assessed and community service referrals are made. Families who do not exhibit symptoms of maternal depression or poor parent–child attachment are assigned to a Parents as Teachers educator (Pfannenstiel & Seltzer, 1989). PAT is a didactic intervention that provides caregivers with parenting support, teaching principles of child development, and addressing psychosocial issues. It is delivered through weekly visitations to the family's home

and continues until the child turns 3 or the intervention goals are fully met. For families with a higher level of need, CPP is provided. Finally, mothers with depressive symptoms may also receive Interpersonal Psychotherapy (IPT; Weissman, Markowitz, & Klerman, 2000).

Preliminary results from BHC have shown that mothers who completed the program exhibited decreased levels of depression, parental rigidity, child abuse potential, difficulty in social relationships, and perceived loneliness. In addition, families in BHC evidenced increased rates of infant immunizations and well-baby visits, and more perceived social support from family members. The willingness of the funders of this program to recognize the importance of continued program evaluation and to commit financial resources to this initiative for almost a decade is particularly noteworthy.

SOCIAL POLICY PERSPECTIVES

The value of translational research leads directly into considerations related to the social policy arena. The personal and economic burden of child maltreatment highlights the importance of utilizing information derived from research to inform policy initiatives. However, despite what should be an almost seamless integration of research, practice, and social policy, reciprocally beneficial interactions among these arenas have been difficult to achieve (Toth & Cicchetti, 2006). In reflecting upon impediments to this integration, Shonkoff (2000) suggested that, whereas scientists are trained to raise questions and to be guided by facts, policymakers are more prone to be governed by political and economic forces. Similarly, service providers are more like policymakers because they are often faced with situations that require immediate action before empirical data are available to inform specific intervention strategies. In reflecting on this tension, Shonkoff (2000) stated, "Science is focused on *what we do not know*. Social policy and the delivery of health and human services are focused on *what we should do*" (p. 182, italics in original). Even when data are available to inform intervention strategies, the realities of heavy clinical caseloads and lack of access to easily assimilable empirical information by clinicians and policy advocates may limit the likelihood of clinicians and policy advocates adopting evidence-based interventions. Unfortunately, over a decade since these observations were made, individuals committed to addressing the problem of child maltreatment continue to struggle to achieve an integration of research, practice, and social policy.

Recently, increased calls have been made for the utilization of science to guide policymaking and funding decisions (Baron & Haskins, 2011; Haskins & Baron, 2011). In fact, the Obama Administration has done much to advance the incorporation of scientific data into policymaking decisions. During his initial inaugural address, Obama stated that an important goal of his Presidency would be to expand social programs that work and to eliminate those that are ineffective (Haskins & Baron, 2011). Early in his Administration, six initiatives to expand evidence-based social programs were launched, including the utilization of home visitation to improve maternal and child health, early childhood development, and family functioning and programs to prevent teen pregnancy (http://www.whitehouse.gov/omb/blog/09/06/08/BuildingRigorousEvidencetoDrivePolicy). Unfortunately, even when evidence exists that a program is ineffective, political forces may make it difficult to eliminate funding for these programs and redirect the funding toward those that are evidence based (Baron & Sawhill, 2010).

In a compelling essay, Haskins and Baron (2011) argued that better population-level outcomes in education, crime reduction, and child well-being would occur if policy and funding decisions were made based on evidence of what works. The call for the utilization of evidence-based approaches, referred to as technocracy, is the norm in physical health care (Dodge & Mandel, 2012). However, in addressing the contrast between health care and issues affecting children, Baron (2007) stated:

> In medicine . . . rigorous evaluations are common, and often drive policy and practice. By contrast, in education and most other areas of social policy, such studies are relatively rare. In these areas, policy and practice tend to be driven more by advocacy studies and anecdote than by rigorous evidence, costing billions of dollars yet often failing to produce meaningful improvements . . . (p. 32).

In view of the magnitude of the adverse consequences of child maltreatment on both psychological and physical health outcomes, it is imperative that policy makers address and remedy difficulties in accessing high quality trauma-informed services. Because evidence-based services for children who have been maltreated are increasingly available (Toth, Gravener, Guild, & Cicchetti, 2013), the failure to ensure their widespread availability is particularly egregious. To reduce impediments to access, partnerships among professionals working with children, elected officials, and public interest advocates are critical (Harris, Lieberman, & Marans, 2007; Toth & Cicchetti, 2006).

It is unlikely that anyone invested in promoting the welfare of children would disagree with the importance of attaining the above stated objectives. Why then has the reduction of the divide among research, practice, and social policy been so difficult to realize? A number of issues

need to be considered, including points of entry to care, allocation of resources, and community-wide uptake.

Entry to Care

Chu and Lieberman (2010) discuss entry points to care for young children exposed to trauma. Although pediatric care providers are the professionals most likely to come in contact with young traumatized children, their effectiveness in identifying possible trauma may be hindered by a number of issues, including the brief visit duration, lack of training in recognizing trauma flags, and minimal knowledge regarding referral sources if trauma is revealed. Mental health providers may similarly lack knowledge regarding the identification of trauma in young children and when trauma is identified they may not have adequate training on the provision of evidence-based models of intervention. Childcare providers also are unlikely to have adequate training on the identification of trauma. Despite the high co-occurrence of domestic violence and child maltreatment, domestic violence shelter staff most typically focus on the needs of adult victims and fail to assess or address the presence of child trauma. Although the court system can mandate treatment for victims of child abuse, court personnel are also unlikely to be adequately versed in understanding the effects of trauma and the need for treatment. Unfortunately, the child welfare system also often focuses on addressing parenting and may fail to consider the needs of maltreated children. When the need for treatment is recognized, far too few professionals are available to provide evidence-based trauma-informed treatments. Fortunately, systemic barriers to access to care can be minimized through large-scale educationally based initiatives that encourage collaborations among professionals from diverse disciplines. One such national initiative, the National Child Traumatic Stress Network (http://www.nctsn.org), has been very successful in increasing the availability of evidence-based services for traumatized children and improving the quality of care for children and families throughout the United States.

Allocation of Resources

Although there has been increased recognition of the importance of supporting evidence-based social programs, political forces that operate do not always act in accord with this goal. The decisions of policymakers are governed by myriad issues, including program cost, input from constituents, the position of party leaders, public opinion, pressure from lobbyists, and their own political philosophies. Far too often, politically favored programs are held intact or allocated increased resources. At times, even scientific evidence that identifies iatrogenic effects of programs is ignored (Barlow, 2010). As we accrue more and more evidence regarding effective prevention and treatment programs for children who have been maltreated, it will be increasingly important that we strive to ensure that research findings are disseminated to and incorporated into the funding decision process. However, that is not to say that funding should be eliminated to support efforts to develop new innovative programs. Unfortunately, it is all too clear that even programs with strong scientific support are not equally effective for all individuals. Moreover, despite decades of research dedicated to evaluating programs designed to foster positive outcomes for children faced with economic and familial disadvantage, many with favorable outcomes, the overall effect sizes for these programs remain within the small to moderate range (Shonkoff & Fisher, 2013). Moreover, some evidence-based models, although shown to be effective for a designated population, address only a small percentage of individuals in need. For example, although the outcomes for the Nurse-Family Partnership home visitation program have been shown to be effective in a number of important arenas, such as improving parental caregiving and child health and preventing child abuse and neglect (Kitzman et al., 1997; Olds, Henderson, & Kitzman, 1994), it limits enrollment to first-time mothers who are identified during their first trimester of pregnancy. Because many young mothers living in poverty do not seek prenatal care, these inclusion criteria result in the ineligibility of significant numbers of very high-risk mothers. Therefore, although we applaud efforts to increase the availability of evidence-based programs, it would be premature to conclude that resources should be directed only toward those programs that have been supported by rigorous evaluation. Rather, funding should be eliminated for programs that have been shown to be ineffective and *resources should be* channeled toward a combination of evidence-based models and innovative approaches designed to address unmet needs or to improve the magnitude of positive outcomes for vulnerable children and families.

Community-Wide Uptake

Most typically, the evidence base for programs is derived from university-based randomized control trials (RCTs). Although these approaches reflect the gold standard in the field, they are not without challenges with respect to dissemination into community settings (Sternberg, 2006; Toth & Manly, 2011). RCTs are conducted under very controlled and often ideal settings, including utilization of strict inclusion and exclusion criteria for participants that make them unrepresentative of those seeking mental

health care in community settings. Unfortunately, and not surprisingly, when such social programs are disseminated into community settings, they yield not only low rates of utilization with respect to individuals eligible for such services, but also tend to be less effective due to issues such as lower credentialed and less experienced providers, lack of supervision, and failure to ensure fidelity of implementation (Dodge & Mandel, 2012). This has been referred to as the scale-up penalty and estimated at 50% (Welsh, Sullivan, & Olds, 2010). Moreover, some changes during dissemination are planned and do not always lead to the intended positive outcome, resulting in considerable variation in the effectiveness of programs provided as part of RCTs and those exported to community settings (Weisz & Jensen, 1999). The way in which an intervention is conceptualized is also very likely to contribute to whether a community is invested in providing it and adhering to its fidelity (Dodge, 2008). Therefore, to promote community uptake, it is critical to consider the ultimate goal of exportation from the initial conceptualization of an RCT. Loosening parameters around the inclusion/exclusion of participants, for example, ultimately might result in the likelihood that the intervention can be disseminated more effectively (Toth, Pianta, & Erickson, 2010). Regardless, despite best efforts to ensure effective implementation of an evidence-based model in community settings, it is critical that evidence on fidelity of implementation and outcomes within a given community be assessed. For this reason, some advocate that legislation should provide a mandate for ongoing evaluation of federally funded programs once evidence-based models have been disseminated to communities and provide the funding to make such evaluation possible (Haskins & Baron, 2011).

Now that we have concluded our discussion of definitional considerations and etiological models of child maltreatment and addressed the psychological and biological sequelae accompanying maltreatment, as well as implications for intervention, translational research, and social policy, we turn our attention toward exciting future opportunities for those committed to continuing the journey to prevent child maltreatment and its deleterious consequences.

THE NEXT GENERATION: NEW FRONTIERS IN CHILD MALTREATMENT RESEARCH

There is now no doubt that the experience of child abuse and neglect, and the accompanying poor quality care, exert a harmful impact on the development and functioning of multiple biological and psychological systems across the life course. However, despite considerable progress in understanding the consequences of maltreatment, important frontiers remain to be discovered.

It is of paramount importance that rigorous and precise definitions of the maltreatment experience be incorporated into all investigations of child maltreatment. Unless this very basic goal is routinely achieved, it will be impossible to move forward in increasing convergent findings related to the sequelae associated with various subtypes and dimensions of maltreatment. Such coherence is particularly important when seeking to translate research from basic investigations into the design and evaluation of prevention and intervention trials.

Studies of psychopathology and mental health have largely neglected the period between adolescence and adulthood (Schulenberg, Sameroff, & Cicchetti 2004). This unfortunate omission is no less true in research that has been conducted on child maltreatment. Although early experience is critical, its influence on subsequent psychopathology and mental health is highly likely to be moderated by later experience (Cicchetti & Tucker, 1994; Sroufe, 1997). The failure to adequately account for the effect that experiences during this critical transitional period may exert on future functioning becomes particularly problematic when the retrospective recall of adults is relied upon to gauge the effects of early maltreatment. The conduct of investigations on the transition to adulthood in individuals with histories of child maltreatment emerges as a largely untapped arena. In this regard, the examination of relevant stage salient mechanisms that may be operative during this period is particularly important. Longitudinal research will be needed to provide vital information about how maltreated adolescents and adults resolve later stage-salient developmental issues such as identity formation, autonomy, the development of personal relationships, intimacy, and work.

Most investigations of the consequences of child maltreatment have examined neurobiological and psychological systems separately. The time has come to emphasize the conduct of longitudinal research that examines biological and psychological systems concurrently over developmental time. In addition to multilevel investigations in basic maltreatment research, the incorporation of multilevel measurement strategies into RCTs of interventions for individuals with histories of maltreatment will be particularly important (Cicchetti & Gunnar, 2008). Such strategies may highlight very divergent mediators and moderators of treatment outcome in individuals with the same disorder who have or who have not experienced

maltreatment. Moreover, determining the multiple levels at which change is engendered through RCTs that incorporate biological and psychological assessments of intervention efficacy will provide more insights into the mechanisms of change and the extent to which neural plasticity may be promoted.

It is important to conduct longitudinal neuroimaging studies of maltreated children and adolescents. Moreover, there is a paucity of neuroimaging investigations that focus on brain function (i.e., fMRI and magnetoencephalography [MEG]) in maltreated individuals. Likewise, it is essential that neuroimaging research includes community samples of maltreated persons. Most of these studies have been conducted on maltreated individuals residing in psychiatric hospitals. These samples present many challenges to disentangling the effects of maltreatment on brain structure and function from other competing conditions (e.g., comorbid psychopathology; substance abuse; medication; psychotherapy).

Although groups of abused and neglected children have been found to differ from groups of nonmaltreated children from similar social class backgrounds on the vast majority of the biological and psychological systems investigated to date, not all maltreated children are affected by their experiences in the same fashion. Despite experiencing significant adversity, there are maltreated children who develop in a psychologically resilient fashion.

Furthermore, the neurobiology of some maltreated children does not appear to be structurally or functionally aberrant and may be reflective of an enhanced neural plasticity in resilient individuals (Cicchetti & Curtis, 2006). It remains to be discovered whether the neurobiological structural and/or functional difficulties displayed by abused and neglected children are irreversible, or, if reversible, whether there are sensitive periods when it is more likely that neural plasticity can occur. In addition, investigations must be conducted that examine whether some neural systems may be more plastic than other neural systems or whether particular neural systems may be more refractory to change, or have a more time-limited window when neural plasticity can occur. Because the brain is a dynamic, self-organizing system that is mutable, future neuroimaging research should strive to ascertain whether the brain structure and functioning of resilient maltreated children differ from those of resilient nonmaltreated children.

Relatedly, because resilience is a dynamic developmental process, it is critical that short- and long-term longitudinal studies on the determinants of resilient functioning are conducted in the future. Resilient functioning is not irreversible. Transitional "turning points" (Rutter, 2012) provide opportunities and challenges for individuals either to remain on a positive trajectory despite ongoing adversity, to "bounce back" from a decline in functioning, to persist on a maladaptive trajectory, or to exhibit a decline in functioning from positive functioning (Cicchetti & Rogosch, 1997). In these longitudinal investigations, resilience should be conceptualized as a multidomain, multidimensional construct. Changes in one domain of competent functioning can cascade to affect other developmental domains over time (Cicchetti & Tucker, 1994; Masten & Cicchetti, 2010). Hence, a longitudinal multiple levels of analysis approach to investigating resilient functioning in maltreated children will help to ensure that resilience processes are examined in a thorough and developmentally appropriate fashion.

Findings from examinations of resilience in maltreated children hold great potential for informing preventions and intervention initiatives (Cicchetti, 2013). When indicators of resilience are identified, they can be incorporated into the development of RCTs. The conduct of longitudinal investigations of resilience will be particularly important in contributing to ensuring that interventions are timed, guided, and implemented as closely as possible to the identification of deviations from adaptive functioning (Luthar & Cicchetti, 2000; Toth & Cicchetti, 1999).

Although we have increased the number of evidence-based interventions that are available to treat children and adults with histories of maltreatment, the dissemination and wide availability of evidence-based models must be expedited. Toward this end, exportation to community settings and the subsequent conduct of effectiveness trials must be a priority for individuals involved with the development and conduct of RCTs demonstrating efficacy. Unless a commitment to dissemination is made upon the completion of successful efficacy trials, valuable treatments may languish in academic settings. In addition, far more evidence-based models are available for treating the aftermath of maltreatment than for preventing its occurrence. Therefore, more attention needs to be directed toward the development of interventions directed toward the prevention of maltreatment. The field also would benefit greatly from research targeted toward identifying factors related to stopping the transmission of maltreatment across generations so that protective factors could be built into interventions for families that are at risk for multigenerational maltreatment.

Future investigations of molecular genetic contributions to resilience also should pay more attention to the process of development (D). For example, GxExD studies

could provide valuable information about how a particular genotypic variant may operate differently depending on the developmental period or environmental context.

We possess virtually no information about the effects of child maltreatment in middle- or upper-socioeconomic environments. Maltreatment clearly transcends social class. Consequently, research on the developmental consequences of child maltreatment and on pathways to resilient adaptation in children raised in nonlow-SES environments is important to conduct to discover similarities and differences in the development of resilient functioning across various social class strata. It would be interesting to ascertain whether family and community protective factors are more likely in middle-SES maltreating families than in maltreating families from the low-SES. Would any of the resources that are more common in nonlow-SES maltreating families result in different pathways to maladaptive or resilient functioning, or to a significantly higher percentage of resilient children? Nonmaltreated children in affluent backgrounds are not immune to developing substance abuse or psychopathology (e.g., depression). Indeed, youth from affluent families can even exhibit more problematic functioning than youth from the low-SES (Luthar & Barkin, 2012). Thus, comparison of maltreated children from different SES backgrounds may shed light on differential pathways to resilient functioning.

In view of the paucity of cohesive findings on race and ethnicity, it will be increasingly important for investigators to conduct research with diverse samples. Moreover, rather than simply utilizing demographics on race and ethnicity in a descriptive manner, examining possible differences among individuals with diverse backgrounds will be particularly important. In this regard, it is equally important to conduct multilevel research on the pathways to resilient adaptation in maltreated children from different cultures.

Maltreatment experiences can exert enduring effects on brain and behavioral development. Epigenetics, the study of heritable changes in gene function that do not alter the DNA sequence, but instead provide an extra layer of transcriptional control that regulates gene activity and plays an important role in the acute regulation of genes in response to environmental changes, is a promising avenue for both basic and intervention research on child maltreatment. Epigenetic mechanisms may explain the stable and dynamic developmental sequelae of maltreatment experiences. Epigenetic research has the potential to serve as a mechanism to explain how maltreatment experiences confer risk for physical and mental health problems.

DNA methylation has been the most studied epigenetic mechanism in research on child abuse and neglect. Alterations in methylation, which manifest as changes in CpG (a site at which cytosine [C] resides next to guanine [G] in the DNA sequence) motifs, may persist in a stable form over a long time. Alterations in the structure of chromatin influence gene expression. Specifically, genes are switched off when chromatin is silent, and they are switched on (i.e., expressed) when chromatin is active. These dynamic states of chromatin are controlled by a number of processes, including epigenetic patterns of DNA methylation. Individual differences in DNA methylation thus are a potential biomarker of the contributions that environmental factors make to the divergence in phenotypes of maltreated individuals who possess similar genetic endowments.

Several investigations have used a candidate gene approach to examine the effects of child abuse and neglect on methylation. Epigenetic regulation is a viable candidate mechanism through which caregiving behaviors, including child maltreatment, may exert long-term effects on HPA activity and neuronal function (Szyf & Bick, 2013). Candidate genes utilized in this regard to date include the serotonin transporter gene, the glucocorticoid receptor gene, and FKBP5 (the binding protein 5 gene; see, e.g., Beach et al., 2009; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). These studies have found that child abuse was associated with increased methylation in both the serotonin transporter and the glucocorticoid receptor genes (see Yang et al., 2013, for a review). Moreover, Klengel et al. (2013) found that FKBP5, an important functional regulator of the stress hormone system, increased the risk of developing stress-related psychiatric disorders in adulthood through allele-specific (i.e., a particular functional polymorphism), childhood trauma-dependent DNA demethylation in functional glucocorticoid response elements of FKBP5.

Most investigations with humans have employed a candidate gene approach to identify specific sites of DNA methylation changes (e.g., see Romens, McDonald, Svarent, & Pollak, 2014). Investigations that have utilized a genome-wide approach have found that these methylation changes occur at many gene loci (see e.g., Labonte et al., 2013; Metha et al., 2013; Suderman et al., 2014). Research with animals who experience abuse demonstrates that experience-induced changes in DNA methylation occur in brain circuits that have functional relevance to trajectories of normal and abnormal behavior. Accordingly, experience-driven DNA-methylation changes in maltreated individuals also have implications for disruptions in neural circuitry and behavior (see Szyf & Bick, 2013; Weder et al., 2014). Likewise, using salivary DNA specimens,

whole-genome methylation differences have been found between maltreated and nonmaltreated children at 2,868 CpG sites. A substantial number of genes implicated in prostate, colorectal, breast, colon, and ovarian cancer were contained in the set of genes that showed differential methylation between maltreated and nonmaltreated children (Yang et al., 2013). These studies each focused on a site-specific gene and collected DNA from lymphoblasts (Beach et al., 2011) or from whole postmortem brain tissue in maltreated adults who committed suicide (McGowan et al., 2009). The results of these investigations suggest that epigenetic mechanisms also may be associated with risk for developing major health problems in later life (Yang et al., 2013).

There is nothing that can be done to prevent the DNA sequence variations that eventuate in the emergence of risky phenotypes. On the other hand, DNA methylation changes in response to experiences such as child abuse and neglect could help to bring about the design, implementation, and multilevel prevention and intervention strategies that change the expression of risky genes through reversal or demethylation and thereby promote healthy physical and mental health development. Szyf and Bick (2013) concluded that DNA methylation adaptations early in life are system-wide and that they involve multiple gene circuits. Thus, because responses to social adversity such as child maltreatment are not limited to the brain and also likely affect peripheral tissues, it is also possible to assess the efficacy of an intervention in peripheral cells.

Prevention and intervention strive to alter the environment to bring about positive outcomes. Research on epigenetics suggests that prevention and intervention also may change the epigenome and that this also could result in improved outcomes. If we are to understand the mechanisms through which early adverse experiences such as child maltreatment impart maladaptation, psychopathology, or resilience, then it is critical that we examine genetic variation (functional polymorphisms) and epigenetic modifications (cf. Klengel et al., 2013).

The knowledge base on the effects of child abuse and neglect has increased exponentially since the early stages of this research were initiated approximately 50 years ago. More recent technological advances open up more avenues for elucidating the mechanisms and processes that contribute to the deleterious consequences associated with maltreatment, and to the development of resilient functioning in the face of adversity, as well as for shedding light on the development and implementation of exciting and effective prevention and intervention strategies.

Although our knowledge on the deleterious effects of child maltreatment on biological and psychological development has burgeoned in recent decades, far too many children continue to be victimized by this pernicious societal problem. Moreover, despite the increased availability of efficacious models of prevention and intervention, the dissemination of these models to communities most in need continues to lag significantly behind the knowledge base. Dissemination of empirically generated results to policy arenas must be expedited if the lifelong scars accompanying child maltreatment are to be addressed adequately.

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CHAPTER 12

A Developmental Psychopathology Perspective on Foster Care Research

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INTRODUCTION

Foster care—the practice of temporarily placing children with nonbiological parents as a way to promote their safety and well-being—is a custom that is likely as old as humanity itself. Allusions to children being cared for by foster caregivers can be found as far back as biblical times in the Talmud and the Old Testament. However, the formal public foster care and child welfare systems in the United States that have been created by regulatory statutes and are administered by federal, state, and county governments are a relatively modern invention, originating in the early twentieth century. How it is that current policies and practices designed to protect vulnerable children and families evolved during the centuries following European colonization of the New World is a matter of some historical interest. Tracing this history is a useful exercise, not only for those who wish to know the origins of family-based care in the United States (as an alternative to institutional care or no care at all), but also for students of typical and atypical child development. An analysis of the historical record reveals many approaches for addressing the problem of parentless children that were identified by observers at the time as clearly not facilitative of positive adjustment. From the emergence of beliefs that children are more than property, to the growth of understanding that childhood is a distinct period of development during which a nurturing environment facilitates well-being across the life span, to commentaries about the high mortality rates in orphanages and recognition of the fundamental needs and rights of children to be reared in families, the evolution of our current foster care system parallels the emergence of the science of psychology.

In this chapter we consider the study of foster care and foster children from a developmental psychopathology perspective. As described by Cicchetti and Toth (2009), this perspective emphasizes a number of key focal points for scientific investigation. In particular, developmental psychopathology seeks to highlight the recursive relationship between research on typical development and atypical development. It uses multiple levels of analysis, from molecular genetics to neurobiology to the individual, family, and society, to examine relevant phenomena. It views prevention and intervention research not only as a way to improve outcomes, but also as a way to understand developmental processes and their underlying neural mechanisms—and as such, as a means for grounding theoretical models of human development. It incorporates conceptualizations of diversity in both process and outcome. Finally, it emphasizes equally the negative outcomes that occur from adverse experiences and the ability of individuals to exhibit significant resilience in the face of adversity.

Our discussion begins with an examination of the roots of the modern foster care system and the origins of research on foster care. We then provide a summary of the extant scientific knowledge base. The chapter concludes with a discussion of future directions for the field.

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A HISTORY OF FOSTER CARE AND FOSTER CARE RESEARCH

In North America, from the early European settlements in the 1600s through colonial times, there were no systematic efforts for providing for the needs of dependent children. Rather, as McGowan (1983) noted in her history of foster care in the United States, many citizens were primarily concerned with sustaining the resources needed for survival and considered children as property; in contrast, the concepts of childhood and children's rights that we may take for granted today were unknown, and the children of paupers and orphans fell under the auspices of the English Poor Laws. This led to a number of possible outcomes for dependent children: being housed in almshouses, becoming indentured servants, being *farmed out* (i.e., auctioned off to citizens who were paid to house them), or staying with their families, who were given minute amounts of subsistence aid. Most commonly, dependent infants and young children were cared for in almshouses until they were old enough to be indentured.

The growth of slavery in colonial America reduced the need for indentured servitude. Moreover, the rise of the abolitionist movement in the early nineteenth century further led to opposition to indentured servitude because it amounted to treating white children in ways that many had come to believe were morally wrong for black children and adults. As such, by the 1830s, institutional care in almshouses became the predominant form of care for children of all ages.

The economic expansion that came after the end of the Civil War was followed by mass industrialization, urbanization, and immigration. These changes and the strongly held religious values in many communities made

it a priority and a possibility to devote resources to caring for the poorest and most needy children and families in America's cities. Newly established private Christian and Jewish philanthropies and public welfare organizations took up the cause of providing support for these individuals. However, care for the needy was still largely provided in orphanages and other institutional settings.

In 1854 Charles Loring Brace, founder of the New York Children's Aid Society, was among a group of social reformers who first identified the propensity for poor outcomes among children in institutional care. Of particular concern to Brace and others was the practice of housing children together with adults, which led to many abuses. Brace and his colleagues promoted an alternative strategy that involved the practice of *placing out* poor and parentless children from eastern cities. These children were put aboard trains and sent to live with families in rural areas in the upper Midwest and upstate New York. The practice proliferated quickly: By one estimate, 40,000 children had been placed out by 1879 (Bremner, 1970–1974).

In addition to the practice of placing out children, the late nineteenth and early twentieth centuries saw the rise of the Children's Home Society movement in the United States. These statewide agencies provided free-of-charge foster placements; like the practice of placing out children, the growth of this movement was rapid. By 1916, there were Children's Home Societies in 36 states. As might be expected, the so-called *orphan trains* and Children's Home Society family placements produced a wide range of outcomes; these practices led to much better lives for some children, while others experienced ongoing neglect and maltreatment (O'Connor, 2004).

The orphan trains and the Children's Home Society movement marked the beginning of a societal shift toward family-based care as an alternative to institutional rearing in the United States (Herman, 2008). Throughout the twentieth century in the United States, opposition to institutional care grew steadily, at least among professionals. For example, the renowned pediatrician Henry Dwight Chapin (1926) noted that mortality rates for children younger than age 2 years in orphanages was exponentially higher than in the general population:

> In 1914 the then American Association for Study and Prevention of Infant Mortality attempted a study of this question. In their review the New York State Department of Charities is quoted as presenting the statistics from 1909 to 1913 of eleven institutions in the State in which the death rate for babies under two years, during this period, based on the total number of children cared for, varied in the different institutions from 183 to 576 per 1,000, with an average mortality rate for the eleven of 422.5 per 1,000. During these same years the death rate for children under two years, based on the estimated population for the state at that age, was 87.4 per 1,000 or about one-fifth of that in institutions. (P. 486)

By the mid-twentieth century, professionals working with the large number of children orphaned and displaced by World War II had repeatedly documented the numerous negative effects of institutional care on children's healthy development (Freud & Burlingam, 1974). During this era, Renee Spitz (1945) coined the term *hospitalism* to refer to children whose growth and functioning had been impaired by long periods of time spent in institutional settings. Psychodynamically oriented research on human attachment by John Bowlby (1953) and animal research examining the effects of maternal separation on rhesus monkeys by Harry Harlow (Harlow & Harlow, 1962) provided further evidence of the importance of a strong bond with a primary caregiver to a child's development and well-being.

Although professionals in the fields of social work, psychology, and pediatric medicine were already strong advocates for foster family care by the mid-twentieth century, institutions remained a very common form of care during this time. Barr (1992) estimated that, in 1910 in the United States, there were more than 100,000 children in institutions and more than 50,000 children in foster care. It was not until 1950 that the number of foster children exceeded the number of institutionalized children.

Although the original foster care programs in the United States were run by charitable and religious organizations, efforts to organize a governmental foster care system did enter the social policy landscape early on. Programs at the federal level can be traced to the first White House Conference on Children in 1909, followed by the establishment of the Children's Bureau in 1912. The Children's Bureau was charged with protecting the welfare of all children in the United States. The New Deal era brought with it numerous federal and state government programs designed to provide a social safety net for the needy, including Social Security. By the 1960s, the growth of these government social welfare programs had led to a formal foster care system funded at the federal level but administered at the state level through a network of county child welfare offices. During the 1960s, the size of the foster care population in the United States began to grow rapidly, a trend that continued through the end of the twentieth century. Indeed, between 1983 and 2000, the foster care population more than doubled in size, from approximately 250,000 children to estimates of close to 600,000 children (U.S. Department of Health and Human Services, 2000).

This trend was attributed to a number of factors: changes in regulations and laws regarding child abuse and neglect reporting, including the passage of the Child Abuse Prevention and Treatment Act (PL93–247) in 1974; more children entering than exiting care; and the combination of increases in poverty, urban and rural substance abuse, and other mental health and social problems in the face of decreasing budgets for social services (Barbell, 1997).

In the years since 2000, the size of the foster care population in the United States has stabilized and no longer appears to be increasing. However, there is increased concern regarding the large proportion of very young foster children, who many consider to be most vulnerable. For a period of time in the 1990s, the number of young foster children was growing at twice the rate of other foster children (U.S. General Accounting Office, 1994), and children younger than 6 years came to represent one-third of the children in care (U.S. Department of Health and Human Services, 1999). While mining several large foster care databases to document these trends, Wulczyn, Ernst, and Fisher (2011) noted that foster children ages 2 years and younger tended to spend more time in care than did their older peers and showed particularly high vulnerability for delayed development.

Notably, in countries outside the United States and especially in developing countries that have historically relied upon institutional care for children in need of out-of-home placements, there has also been some growth in the use of foster care. As we discuss elsewhere in this chapter, this development may be in part a response to widespread documentation—much of it from the scientific literature—that the absence of a primary caregiver that occurs in the case of institutionalized rearing produces the worst outcomes possible. As such, the use of foster care as an alternative to institutional care must be viewed as a positive development.

Foster Care Research

For almost as long as foster care has been an organized system of care in the United States, it has been the subject of systematic research. The first known empirical study of foster care outcomes (van Senden Theis, 1924) examined outcomes from close to 1,000 children placed in care by the New York State Charities Aid Association during the previous 2.5 decades. The study found what numerous subsequent investigations have continued to replicate (e.g., Clausen, Landsverk, Ganger, Chadwick, & Litrownik, 1998; Glisson, 1994, 1996; Halfon, Mendonca, & Berkowitz, 1995; Pilowsky, 1995; Trupin, Tarico, Benson, Jemelka, & McClellan, 1993; Urquiza, Wirtz, Peterson, & Singer, 1994): Foster children fare far better than children who remain in maltreating families but manifest poorer adjustment and increased problem behavior compared with nonmaltreated children.

Despite remarkably consistent evidence that foster children lag behind their peers on most measures of development and well-being, the policies and programs designed to address the needs of foster children have been almost continuously in flux. McGowan (1983) observed that child welfare policies have been akin to a pendulum swinging back and forth along a number of key dimensions. They include the rights of parents to maintain their family with integrity versus the vulnerability of children and their need for protection; the need to provide families with support versus the need to keep children safe; federal responsibility versus state, local, or individual family responsibility for the care of the child; public versus charitable and philanthropic funding for services; services to support children's development versus services to prevent harm; family preservation versus child-centered services; maintaining clearly defined boundaries among services designed to meet the needs of families (e.g., child welfare, family service, juvenile justice, other services) versus integrating services within systems of care; patient- or client-centered approaches to intervention tailored to the specific needs of the individual versus uniform standards of treatment; and specialized professional services versus paraprofessional, community-based supports. One explanation for the fluctuations in policies has been the lack of penetration of scientific knowledge about child development, and the needs of foster children in particular, into legislative settings. This has begun to change as researchers have endeavored to engage in translational communications designed to be useful in programmatic decision making and resource allocation, and policy makers have embraced evidence-based practice as a standard of care. Whatever the explanation for the historical instability of policies, however, although we tend to think of the latest trends in foster care services as novel and innovative, and although vast resources are regularly put into reengineering public child welfare systems, few trends have not been the focus of prior reform efforts, and no approach or combination of approaches has substantially reduced the disparities found among foster children.

Over and above documenting the trends in foster care and the ongoing needs of the children and families involved, and germane to the subject of this chapter, research on foster care provides a window into how extreme variations in typical early rearing experiences

affect development. Although animal models involving rodents and primates have provided extensive information in this area, only a few other contexts in research on human development (e.g., adoption) allow such questions to be investigated empirically. Similar to research on the broader topic of child maltreatment, research on foster care can delineate how variations in specific dimensions of adversity affect the trajectories of children's lives; in addition, this work can uniquely inform us about how the alterations in the caregiving environment that occur with placement in care and subsequent caregiver transitions, including reunification with birth parents and subsequent foster placements, mitigate or compound the effects of adversity. As such, this work informs our understanding of which behavioral, cognitive, and biological systems are most pliable (and, thus, affected positively or negatively) at specific times during the course of development. In addition, prevention and intervention research in this area is helping to inform our understanding of the best strategies to use to maximize opportunities for recovery from early adversity. Finally, and perhaps most remarkably, research on foster care informs our understanding of typical development under the most adverse conditions and which intrinsic and environmental factors buffer individuals from experiences that would ordinarily disrupt health and well-being.

The remainder of this chapter focuses on a developmental psychopathology perspective (Cicchetti & Toth, 2009) on how research on foster care can increase our understanding of typical and atypical development. A great deal of literature pertains to this topic—for example, searching *foster care* on the PsycNET scientific database results in more than 5,000 empirical publications between 1950 and the present. As such, it can be challenging to synopsize the scientific knowledge base in this area, and we strongly emphasize that this chapter is not intended to be an exhaustive review of the field of foster care research. We acknowledge that the organizational scheme we have used is somewhat arbitrary and some readers will undoubtedly fail to incorporate *all* important domains. Moreover, with respect to much of the research in this area, it is often not possible to disentangle the effects of maltreatment and other forms of adversity from the effects of placement in foster care, which itself may conflate factors such as separation or loss with the effects of care by nonbiologically related adults. In short, there are clear limitations to the amount of scientific control that can be applied to investigations in this area. Consequently, we fully expect this summarization of a developmental psychopathology perspective on foster care research will be updated, extended, and broadened in future discussions. With these qualifications in mind, we assert that foster care research provides evidence that:

- Early adversity increases the likelihood of atypical emotional, psychological, and cognitive development.
- Early adversity has the potential to alter biological development and to increase risk for disease.
- The timing and duration of adversity is associated with differential outcomes, with a general trend of longer lasting adversity producing the most profound effects.
- Neglect is a particular cause for concern because of its pervasiveness and its propensity to disrupt healthy development and exert a lasting impact on health and well-being.
- Transitions among primary caregivers are a specific class of adverse experience worthy of attention because they appear to negatively affect the development of key cognitive and behavioral skills needed for social and academic success.
- The combined effects of prenatal stress, especially prenatal substance exposure, and early adversity on neurobehavioral development are additive and produce worse outcomes than do prenatal stress or early adversity alone.
- Resilience (i.e., typical development in the face of adversity) is evident in all samples of foster children, although what contributes to it is not well understood.
- Family-based care, including foster care, is as a general rule better than institutional care.
- Systematic, well-timed, family-based interventions have the potential to mitigate the effects of early adversity on healthy development.

The next section elaborates upon each of these topics. A unifying discussion follows that includes future directions and implications for research in the emerging field of translational neuroscience.

EARLY ADVERSITY INCREASES THE LIKELIHOOD OF ATYPICAL EMOTIONAL, PSYCHOLOGICAL, AND COGNITIVE DEVELOPMENT

Perhaps the strongest conclusion that can be drawn from foster care research with respect to development is that it provides convergent evidence, along with evidence from many other areas of research, that early adversity alters typical life-course trajectories in a negative manner. This is consistent with a large body of animal research on the effects of adverse rearing conditions (Levine, 2005)

and research on child maltreatment (Cicchetti, 1996; Toth & Cicchetti, 2013). It is also consistent with research on other forms of human adversity, such as poverty (Duncan, Magnuson, Kalil, & Ziol-Guest, 2012; Duncan, Ziol-Guest, & Kalil, 2010). Put simply, foster children as a group consistently lag behind their peers on measures of development and show poorer psychological adjustment (Pears & Fisher, 2005a, 2005b). In this section, we summarize the research on psychological, developmental, and cognitive problems that have been observed among foster children.

Mental Health Outcomes

One of the best-investigated domains in this area is foster children's mental health. The National Survey of Child and Adolescent Well-Being (NSCAW) is a landmark study that provides some of the most compelling evidence of the disparities of foster children in the United States in this area. The NSCAW is a nationally representative sample of more than 6,000 children and families who have been investigated by public child protective services programs in the United States between 1997 and 2014. This study was funded by the U.S. Administration of Children and Families and has produced a multitude of technical reports and peer-reviewed publications to date. Two cohorts of children were recruited into the NSCAW study, and information was gathered from the children, their parents, other caregivers, caseworkers, teachers, and administrative records.

Analyses of the NSCAW dataset have revealed that emotional and behavioral problems are present in more than 50% of the children in the sample (Burns et al., 2004). Numerous other publications using the NSCAW data set have documented the prevalence of specific mental health problems in this population (e.g., Casanueva, Cross, Ringeisen, & Christ, 2011; Orton, Riggs, & Libby, 2009; Southerland, Casanueva, & Ringeisen, 2009)

High rates of mental health problems in foster children are not specific to the United States. Rates in Norway have been shown to be similar to those observed in the NSCAW study; for example, one in two children out of a sample of 279 foster children have been shown to exhibit some form of mental health disorder (Lehmann, Havik, Havik, & Heiervang, 2013). Similarly, English foster children have been shown to exhibit close to four times higher rates of mental health disorders than children living in economically disadvantaged families (Ford, Vostanis, Meltzer, & Goodman, 2007). Similar patterns of mental health disparities among foster children have been found throughout Europe (Holtan, Ronning, Handegard, & Sourander, 2005), Australia (Sawyer, Carbone, Searle, & Robinson, 2007), and Canada (Legault, Anawati, & Flynn, 2006).

Externalizing disorders appear to be one of the most common forms of psychopathology among foster children. For example, Garland et al. (2001) surveyed children receiving services within a number of public-care institutions (e.g., child welfare, juvenile justice, public school services for youths with serious emotional disturbances) and found that the most prevalent disorders were attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders (e.g., oppositional defiant and conduct disorder). The foster care portion of this larger sample comprised 426 children, of whom 38.7% displayed ADHD or a disruptive behavior disorder; overall, externalizing disorders accounted for a much higher percentage than did anxiety or mood disorders, which were present collectively in only 13.8% of the foster children.

While externalizing mental health disorders are more prevalent among foster children, rates of internalizing disorders also appear to be higher for foster children than for their community counterparts to a meaningful extent. For example, when 373 older foster children were interviewed for a study, the prevalence rates of major depression were revealed to be greater than those of a sample of working-class 18-year-old community youths. Depending on the early adversity the foster child had experienced prior to entering out-of-home care, the percentage of individuals suffering from major depression changed: 23% for physical abuse, 22% for physical neglect, and 26% for sexual abuse (McMillen et al., 2005).

These findings are congruent with those from other studies that have found an elevated risk for lifetime major depression in foster children compared with nonfoster children and an increase in suicidal ideation and attempts related to feelings of unimportance and inferiority within the child (e.g., Pilowsky & Wu, 2006). It should be noted, however, that not all data on internalizing disorders are consistent. Some studies have found no differences between scores of depression of foster children and published norms, relevant to the Children's Depression Inventory on children between ages 8 and 16 years (Allen, Combs-Orme, McCarter, & Grossman, 2000).

Trauma-related anxiety disorders are also common among foster children who had experienced some form of sexual abuse or multiple forms of abuses. A comparison between sexually abused, physically abused, and nonabused foster children revealed that more than 60% of sexually abused children exhibited posttraumatic stress disorder (PTSD) and that physically abused children had a higher prevalence for PTSD than did nonabused children, at a rate of one in five (Dubner & Motta, 1999). When compared with a community comparison sample, foster children who had experienced maltreatment, including

neglect, had 1.75 times the risk for manifesting PTSD (Widom, 1999).

Other problem domains include sexual behavior and eating difficulties (Tarren-Sweeney, 2006). For example, using the Assessment Checklist for Children, Tarren-Sweeney & Hazell (2006) found that approximately 33% of their sample of foster and kinship children ages 4–9 years exhibited age-inappropriate sexual behavior. Two prominent trends exist in terms of food-related difficulties as a result of early adversity: food maintenance syndrome and pica-type eating behavior. Tarren-Sweeney (2006) examined these patterns in a study of 347 preadolescent children and found that 24% displayed clinically significant eating difficulties. The eating difficulties tended to be associated with developmental profiles. For instance, those displaying food maintenance syndrome were comorbid with psychiatric disturbances, specifically, disruptive behaviors and affective problems, and pica-type eating behavior was associated with developmental problems ranging from intellectual disability to speech and reading problems (Tarren-Sweeney, 2006).

Attachment and Social Functioning

Research on foster care also provides support for the association between early adversity and problems with social functioning, especially in terms of caregiver attachment (Stovall-McClough & Dozier, 2004) and peer relationships (Leve, Fisher, & DeGarmo, 2007). Reactive attachment disorder and disinhibited attachment disorder are common forms of atypical attachment that have been observed when youths are exposed to early adversity. At the time of initial placement for foster children (ages 1–4 years), for example, Zeanah et al. (2004) found that 37% were diagnosed with reactive attachment disorder, 22% were diagnosed with disinhibited attachment disorder, and 17% were diagnosed with both disorders. An additional study showed similar findings. In a comparison between foster children and nonmaltreated, school-age children, higher rates of reactive attachment disorder were found among the foster children (Minnis, Everett, Pelosi, Dunn, & Knapp, 2006). One factor that was found to be associated with increased risk of developing reactive attachment disorder was increased numbers of placements for the foster child (Lehmann et al., 2013).

In addition to these general patterns of atypical social functioning, young foster children show a propensity to be indiscriminately friendly toward others, readily approaching unfamiliar individuals and showing little social reserve (Pears, Bruce, Fisher, & Kim, 2010). This pattern has also been observed among children reared in institutional settings (Gleason et al., 2014; Rutter et al., 2010); however, it is important to note that studies of both populations have shown that indiscriminate friendliness, while associated with problems in inhibitory control, is not correlated with attachment difficulties (Bruce, Tarullo, & Gunnar, 2009; Pears, Bruce, et al., 2010). Thus, as is discussed later in this chapter, this atypical pattern of behavior may be most accurately characterized as a neurobehavioral difficulty associated with social development than as an attachment problem.

A Canadian study examined the psychological adjustment of foster children, specifically, their anxious behavior and physical aggressiveness in the context of caregiver relationships (Legault et al., 2006). More permanent and higher quality caregiver relationships resulted in less frequent physical aggression, increased number of close friends, greater self-esteem, the use of approach coping strategies, and less frequent avoidant coping strategies and attachment behaviors.

Cognitive Functioning Deficits and Academic Adjustment

Foster children also show deficits in a variety of domains of cognitive functioning. More than half of foster children are estimated to have cognitive difficulties (Landsverk, Davis, Ganger, Newton, & Johnson, 1996). Many of these deficits have been found to be a direct result of early adversity, including early separation from the biological parent, multiple placements, neglect, and abuse. For example, Mueller et al. (2010) found that early adversity experiences were associated with altered cognitive ability when maltreated adopted children were compared with their typical adolescent counterparts on a change task experimental paradigm that tests one's ability to inhibit responses: the adopted children showed impaired cognitive control after having experienced early adversity.

Preschool-age foster children exhibit specific cognitive deficits, including poorer visuospatial processing, poorer memory skills, lower scores on intelligence tests, and less developed language capacities (Pears & Fisher, 2005a). Visuospatial processing was found to be associated with type of abuse and the number of maltreatment types: The ability to process visuospatial information increased with number of maltreatment types and decreased with neglect or emotional abuse. These unexpected patterns offer an early understanding of how the developing mind reacts to maltreatment and abuse.

Language is important to success in multiple realms of development because of its use as a tool for expression and communication (Stock & Fisher, 2006). In contrast, language deficits can lead to poor academic adjustment, which has been shown to increase mental health and behavioral problems, including internalizing and externalizing

problems (Halonen, Aunola, Ahonen, & Nurmi, 2006). Before children have the ability to read, their phonological awareness in kindergarten is one of the most predictive prereading skills. Pears, Heywood, Kim, and Fisher (2011) examined phonological awareness among foster children entering kindergarten: up to 54% scored below the 23rd percentile, indicating a risk for later reading difficulties and other academic challenges.

Poor academic adjustment is also a common problem among foster children. For example, when researchers looked at more than 11,000 second-grade children, they found that compared with community children, those in out-of-home placements showed a higher prevalence of school suspensions and experienced higher rates of poor academic achievement (Fantuzzo & Perlman, 2007; Mitic & Rimer, 2002).

Developmental Delays

The preceding review of social and cognitive functioning deficits in foster children clearly indicates that developmental delays are also very common among foster children. For example, one study compared prevalence rates of developmental delays between children in the general population and foster children and found a 4% to 10% rate in the general population and rates as high as 60% in foster children (Leslie, Gordon, Peoples, & Gist, 2002). When Klee, Kronstadt, and Zlotnick (1995) examined the psychomotor development of 125 children ages 0–3 years, they found that 50% of the foster children rated below the typical level of psychomotor development for their age group, compared with 13% in the normative sample.

Demographic and Race/Ethnicity Differences

Some noteworthy differences exist between male and female foster care alumni. Female foster care alumni are at not only heightened risk for multiple pregnancies, but are at higher risk than are their male counterparts for maltreating their children. Educational outcomes differ, as well. When Dworsky and DeCoursey (2009) examined a sample group of 4,590 pregnant or parenting foster care alumni from metropolitan Chicago, they found that only 44% of the females and 27% of the males possessed a high school diploma or graduate equivalent degree when they exited the program.

The race/ethnicity of foster families and children has been shown to be less influential in determining mental health outcomes among foster care alumni (Villegas & Pecora, 2012). For Caucasian, Hispanic/Latino, and African–American individuals who had experienced some form of foster care, ethnic background was not a strong predictor of whether mental health services would be needed later in life. However, gender, age of entrance into foster care, number of placements, and maltreatment before and while in foster care were factors associated with the eventual need for mental health services (Villegas & Pecora, 2012). It is noteworthy that there is relatively limited research in this area, however; this is a concern in part because of the overrepresentation of racial and ethnic minorities in foster care.

Long-Term Effects

Evidence suggests that the impact of early adversity on psychological and emotional well-being among foster children is not transitory and can persist well into adulthood. In a study in England, for instance, researchers found that adults who had spent time in foster care had twice the rates of mental health, drug, or alcohol problems than those with no histories of foster care (Viner & Taylor, 2005). Similarly, among a sample of 19,430 foster children ages 12–17 years, foster children were shown to have much higher rates of alcohol and illicit drug use (Pilowsky & Wu, 2006). The problems observed also extend to antisocial and criminal behavior. For example, among the NSCAW sample, arrests had occurred at more than four times the national rate for individuals ages 18–24 years (Administration for Children and Families, 2008). In addition, compared with their community peers, youths aging out of foster care have been shown to display higher rates of criminal and delinquent behaviors ranging from minor infractions to more serious crimes (Cusick & Courtney, 2007).

To summarize, the research suggests that foster children show alterations in development across many domains of mental health and well-being. There are few instances in which, when compared with nonmaltreated community children, foster children haven't been found to show disparities. This cumulative body of evidence supports the conclusion that early adverse experiences exert pervasive and enduring influences on typical development.

EARLY ADVERSITY HAS THE POTENTIAL TO ALTER BIOLOGICAL DEVELOPMENT AND TO INCREASE RISK FOR DISEASE

The notion discussed in the previous section—that early adversity affects typical mental development—has been a mainstay of the field of psychology dating back to the

early psychoanalysts. Similarly, there is a long tradition of research on the effects of stress on biological development dating back to the seminal work by Hans Selye (1936). Selye described a general adaptation syndrome in which the body goes through a series of stages in response to chronic stress, including alarm, resistance, and finally exhaustion. This helped explain the prevalence of illness and other negative sequelae in animals (and humans) exposed to chronic adversity. Although Selye's ideas have received considerable revision and clarification in the ensuing decades, many of the core ideas encompassed in his theory remain.

A vast animal literature about this topic shows the impact of stress on cognitive development and on neuroendocrine, immune, and metabolic systems (Levine, 2005). Much of this work has used paradigms that disrupt the early rearing environment of the species under investigation, most commonly through separating the offspring from its parent or by creating stress in the environment of the mother and her offspring. These studies have led to the fairly incontrovertible conclusion that stress experienced early in life has the potential to compromise the physiology of an organism at many levels.

Whereas research involving animals has provided an extensive and precise knowledge base regarding the timing, type, and duration of adverse experiences on typical development, the human literature about this topic is, understandably, considerably more limited because of the unfeasibility of exerting the degree of experimental control on specific dimensions of adversity that has been used in animal studies. However, as described in the next sections of this chapter, researchers have extensively documented the atypical physical, brain, and biological development in populations that have experienced early adversity.

Neuroendocrine Effects of Adversity

The primary neuroendocrine regulation system known to be affected by early adversity is the hypothalamic-pituitary-adrenal (HPA) axis, which is believed to contribute to a number of neurocognitive and physical health outcomes (Chrousos, 2009; Pechtel & Pizzagalli, 2011). In this system, physical or psychological stressors, including separation from a primary caregiver in infancy or social threat in late childhood, trigger a neuroendocrine cascade. Specifically, with sensory input and input from other areas of the brain indicating a disruption in homeostatic balance, corticotrophin releasing hormone, or CRH, is released in the hypothalamus. CRH is transported to the anterior pituitary, where it stimulates the release of adrenocorticophin releasing hormone, or ACTH; ACTH then enters the bloodstream and stimulates the release of glucocorticoids in the adrenal cortex. The release of these glucocorticoids (cortisol in humans, corticosterone in rodents) signals the widespread engagement of additional resources throughout the body to respond to environmental stressors, including increased metabolic rate and immune function (Chrousos, 2009; Hostinar, Sullivan, & Gunnar, 2014; Pechtel & Pizzagalli, 2011). In this way, cortisol released from the HPA axis plays a number of key roles in helping maintain a balance in response to perturbations (Chrousos, 2009). Under normative (nonmaltreating) environmental conditions, activation of the HPA axis in response to acute stressors is considered adaptive; however, environments with excessively high levels or chronic exposure are believed to reach harmful, *toxic* stress levels (Shonkoff, Garner, et al., 2012).

The HPA axis also exhibits a diurnal rhythmicity (Kirschbaum & Hellhammer, 1989). In humans, cortisol levels are very low during the night, begin to rise around the time of awakening, and reach their daily peak approximately 30 minutes after awakening. Levels then drop off fairly precipitously and continuously throughout the morning, and reach their nadir from bedtime through the night. Although this pattern is not established in infancy until children develop regular day/night sleep cycles, it does appear to remain fairly stable once established. One exception is that when individuals undergo periods of chronic stress (e.g., a health crisis, divorce, college exams), cortisol levels may fail to decrease, and instead, remain elevated throughout the day.

Research evidence has documented adversity-related alterations in the typical diurnal pattern of HPA-axis activity. Specifically, a *blunted* pattern is commonly observed in maltreated children, including foster children, that characteristically involves low morning cortisol levels that remain low throughout the day or a smaller decline across the day from morning to evening (Bruce, Fisher, Pears, & Levine, 2009; Trickett, Noll, Susman, Shenk, & Putnam, 2010). Although the specific mechanism for this blunted diurnal pattern, termed *hypocortisolism*, among foster children is not known, it may represent a down-regulation of the HPA-axis system as a resource-conservation mechanism in response to chronic early adversity (Fisher & Gunnar, 2010; Hostinar et al., 2014). Similarly dysregulated HPA-axis function has been observed in institutionally reared children (Carlson & Earls, 1997; Gunnar, Morison, Chisholm, & Schuder, 2001). Notably, improved environments, including adoption from institutional care or therapeutic foster care interventions, have been found to

normalize diurnal cortisol patterns in maltreated children or prevent further dysregulation from occurring (Fisher, Stoolmiller, Gunnar, & Burraston, 2007).

Substantial evidence from the animal literature suggests there are pathways through which dysregulated cortisol patterns may confer broader risk to the organism. Specifically, the function of brain regions dense with glucocorticoid receptors (e.g., prefrontal cortex, hippocampus, amygdala) are particularly compromised following acute and chronic stress exposure (Hostinar et al., 2014; Pechtel & Pizzagalli, 2011). Some evidence suggests that chronic stress and cortisol dysregulation relate to cellular atrophy in some of these regions (e.g., prefrontal cortex) and the opposite (i.e., increased cellular structure) in other regions, such as the amygdala (related to fear-based learning). These changes are theorized to contribute to a decreased capacity for adaptive homeostasis in the HPA-axis system and resulting stress sensitivity (Hostinar et al., 2014).

Although less established in the literature, the neuroendocrine regulation of the oxytocin hormone, which is involved in human bonding and social behavior, may also be altered by early adversity. This hormone is predominantly synthesized in a hormonal cascade similar to that described for the HPA axis. In this case, the cascade begins in the hypothalamus and proceeds through the pituitary and peripheral organs (e.g., uterus, testis, heart; Hostinar et al., 2014). Although there are no studies of oxytocin in foster children, inferential evidence can be obtained about the effects of early adversity on this hormone from related areas of the literature. For example, in comparison with nonadopted children, children who were adopted following early institutionalized care show lower levels of urinary oxytocin when interacting with their mothers (Wismer Fries, Shirtcliff, & Pollak, 2005). In addition, oxytocin levels in the cerebrospinal fluid of adult women with a history of maltreatment have been shown to be lower than those of controls with no such histories (Heim et al., 2008).

The Effects of Early Adversity on the Structure and Function of Brain Regions

A wide variety of brain regions important to basic and complex cognitive skills (e.g., self-regulation) appear particularly susceptible to environmental experiences because of their protracted course of development and stress-sensitive neurochemical properties (Berkman, Graham, & Fisher, 2012; Pechtel & Pizzagalli, 2011). Research evidence about the impacts of early adversity on these brain regions suggests alterations in the structural properties of the brain and functional correlates in neuroimaging and electrophysiological studies. It is important to note, however (as we present later in this chapter), that with a few noteworthy exceptions (e.g., Bruce et al., 2013), this research base is drawn from populations that are overrepresented in foster care, but in many cases it is not specific to research on samples of foster children.

A key developmental marker of healthy brain development is an increase in white-matter density and integrity, reflecting myelination and the insulation of neural pathways. Increased white-matter density and integrity, particularly originating from prefrontal brain regions, is believed to reflect the adaptive refinement of neural networks through heightened connectivity and integration within and between brain regions and circuits (Pechtel & Pizzagalli, 2011; Uddin, Supekar, Ryali, & Menon 2011). However, early adversity in the form of maltreatment has been found to alter white matter, with severe institutional neglect predicting whole-brain white-matter reductions and specific reductions in tracts within prefrontal brain regions and between prefrontal and temporal cortices (Hanson et al., 2013; McCrory, De Brito, & Viding, 2012). Children who have experienced maltreatment and show PTSD symptomatology, in contrast, have been shown to exhibit specific white-matter reductions in prefrontal brain regions but no whole-brain differences in white-matter integrity (DeBellis et al., 2002). The corpus callosum comprises the largest white-matter structure in the brain and has been found in all but one study of maltreated children to have adversity-associated reductions in white-matter integrity (McCrory et al., 2012). This cross-hemispheric brain structure is involved in a number of higher cognitive abilities (e.g., executive function, emotion). Atypical development of the corpus callosum has been theorized to contribute to the cognitive impairments found in maltreated children, although this association has yet to be established (McCrory et al., 2013).

Research evidence about the effects of early adversity on gray-matter volume in the cerebral cortex, which reflects neuronal density, is less consistent, with different studies reporting adversity-related increases or decreases in gray-matter volume (DeBellis et al., 2002; McCory et al., 2012). These discrepancies may result from the inverted U-shaped trajectory of gray matter over the course of development—specifically, early increases followed by a decrease in adolescence and relative stability in adulthood (Pechtel & Pizzagalli, 2011). Combined with developmental increases in white-matter density, these *cortical thinning* processes are believed to reflect the refinement of neural networks and the establishment of more efficient processing

that facilitates advanced cognitive skills (Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011). Because of this nonlinear trajectory of gray-matter development, *altered* development could be reflected in multiple ways—for example, a lack of experience-related neuronal growth, resulting in reduced gray-matter volume, or insufficient gray-matter pruning, resulting in increased gray-matter volume. Interpreting the existing literature in this area is further hindered by the heterogeneity of maltreatment experiences, the differing sample age groups studied, and the differing timing of adversity across studies (McCrory et al., 2013).

The results for gray-matter integrity of noncortical brain regions are somewhat more consistent, with reductions in cerebellum gray-matter volume reported in multiple studies of children and adolescents with a history of maltreatment and adversity (McCrory et al., 2013; Pechtel & Pizzagalli, 2011; Teicher, Tomoda, & Andersen, 2006). Hippocampal-volume reduction is also associated with a history of adversity, although this difference does not appear to emerge until later adolescence or early adulthood. Although this reduction may be exacerbated by adversity-related high-risk behavior, such as alcohol abuse, findings from human and animal studies suggest that it also occurs as a consequence of early adversity itself. In rodent models, this has been posited to arise from alterations in expected prepubertal gray-matter overproduction and subsequent postpubertal pruning processes, resulting in a net deficit in hippocampal cells (Teicher et al., 2006).

Findings from research conducted during challenging cognitive tasks also provide evidence for the impacts of early adversity on the function of prefrontal and hippocampal brain regions. Such research uses functional MRI (fMRI) to measure regional blood-flow activity during performance of computer tasks, including protocols that assess the neural bases of inhibitory control (i.e., the ability to stop a planned motor response) and working memory (Bruce et al., 2013; Carrión, Haas, Garrett, Song, & Reiss, 2010; Mueller et al., 2010). In experimental paradigms involving inhibitory control, young maltreated adolescents in foster care were found to have less fMRI activation than did controls in prefrontal brain regions associated with inhibitory control (e.g., anterior cingulate cortex) and in visual processing brain regions (e.g., occipital cortex; Bruce et al., 2013). However, these findings somewhat contrast with the findings from another study of young adolescents with severe institutional neglect: these adolescents were found to have greater activation in prefrontal brain regions (e.g., inferior frontal cortex, anterior cingulate cortex, striatum) for inhibitory control versus non–inhibitory control trials (Mueller et al., 2010). Although both studies provide evidence that early adversity affects functionality in the neural substrates of advanced cognitive skills, the conflicting directionality of the findings has yet to be reconciled in the literature. Measures (fMRI) of brain activation during a working-memory task have also been examined in children and adolescents exhibiting PTSD symptomatology following early interpersonal trauma (e.g., physical abuse, sexual abuse, witnessing violence; Carrión et al., 2010). Such findings suggest that the participants who had experienced adversity had significantly less hippocampal activation during memory retrieval compared with participants who had not experienced adversity. This reduced activation was also found to be related to PTSD symptoms, particularly in the avoidance/numbing cluster, further strengthening the potential implications of hippocampus hypoactivation as a potential link to memory abnormalities associated with early adversity (Carrión et al., 2010).

Event-related potential (ERP) research has provided additional support for atypical functioning in prefrontal brain regions during challenging cognitive tasks. This research measures average electrophysiological activity at the scalp, which relates to specific task events and associated cognitive processes. Across samples facing early adversity (i.e., foster children and severely neglected institutionalized children), there is converging evidence that children exhibit slower executive attention–related ERP components that involve prefrontal attention processes (e.g., the N200; McDermott, Westerlund, Zeanah, Nelson, & Fox, 2012). This delayed neurocognitive response has been theorized to reflect a slower processing speed and has been associated with longer trial-reaction times. Early adversity has also been associated with reduced ERP responses related to attention and inhibitory control (e.g., the N200 and the P300), which have been theorized to reflect attention-regulation difficulties (Loman et al., 2013; McDermott et al., 2012). Although the aforementioned ERP components likely have multiple neural generators, prefrontal brain regions are critically implicated and theorized to coordinate activity across neural networks (Baumeister et al., 2014; Huster, Westerhausen, Pantev, & Konrad, 2010).

The growing body of ERP research findings also suggests that prefrontal brain regions (e.g., anterior cingulate cortex) in children who have experienced early adversity function atypically during tasks that require performance monitoring (Bruce, McDermott, Fisher, & Fox, 2009; McDermott et al., 2012). *Performance monitoring* refers to increased attention to errors in performance on a given

task and may include internal monitoring (internal awareness that an error has been made) and external monitoring (processing feedback that indicates the presence of an error). Specifically, during computerized inhibitory control tasks, children in regular foster care were shown to lack the expected ERP response following errors in performance versus correct trials. Notably, the adversity-related reduction in cognitive performance monitoring has been found for both internal and external monitoring processes. However, the children in therapeutic foster care (with additional intervention services) exhibited the expected exaggerated ERP response to errors for internal and external monitoring processes; this suggests that children who have experienced early adversity have the capacity for more normative cognitive processing in the presence of intervention and supports.

The neurocognitive processing of emotional stimuli has also been shown to differ among children with histories of adversity. Across a wide range of ages (e.g., 15 months to 9 years), ERP research findings indicate that adversity is associated with exaggerated, later stage attentional processing of angry stimuli, including angry (vs. happy) faces and voices (Curtis & Cicchetti, 2013; Shackman, Shackman, & Pollak, 2007). Research findings using fMRI have also shown an exaggerated right amygdala response to angry faces in maltreated children compared with controls (Dannlowski et al., 2012). Multiple contributing factors have been proposed to understand these findings, including increased exposure to anger in adverse environments and hypervigilance to threat (Curtis & Cicchetti, 2013; Shackman et al., 2007). Research in the early stages of attentional processing has also shown evidence for the increased processing of happy faces in maltreated children, which has been theorized to reflect the heightened processing of emotional stimuli as an adaptation to emotional stress (Curtis & Cicchetti, 2013; McCrory et al., 2013).

Other Physical Effects of Adversity

Beyond documenting the effects of early adversity on neurobiological regulatory systems, findings from research on foster care also indicate that some of the most basic functions are disrupted by perturbations to the early environment. For example, researchers have found that young foster children show signs of so-called *failure to thrive*, as indexed by a shorter stature and a smaller head circumference compared with that of typical children (Pears & Fisher, 2005a). As with the aforementioned study findings, these findings match those obtained in investigations of post–institutionally reared children and highlight the profound alterations that early adversity has on a child's physical, brain, and biological development.

The large-scale, population-based Adverse Childhood Experiences Study (ACES) has illuminated the general gradient between the cumulative number of adversity categories that an individual has suffered and the deleterious effects on many domains of adult health and well-being (Anda et al., 2006). In this study, the measure of adverse experiences included childhood maltreatment and general household dysfunction (e.g., adult in household with mental illness, incarceration, substance use problems, suicide, violence against the mother). The cumulative-risk approach used by the ACES investigators is particularly useful given that childhood adversity categories typically co-occur at rates as high as 80% to 98% (Dong et al., 2004; Pears, Kim, & Fisher, 2008).

A range of health problems has been found to be overrepresented in population-based survey data in samples of adults with four or more adversity categories (Felitti et al., 1998). They include heart disease, obesity, high blood pressure, allergies, arthritis, asthma, circulation problems, ulcers, chronic pain, and cancer. However, not all studies have found increased risk for every health problem (Chartier, Walker & Naimark, 2010; Felitti et al., 1998; Springer, Sheridan, Kuo, & Carnes, 2007).

A challenge in interpreting the causal links between childhood experiences and poor adult health in population-based studies is the fact that ACES also includes risk for adulthood-specific, health-threatening behavior (Arnow, 2004; Felitti et al., 1998; Springer et al., 2007). In addition, epidemiological research findings suggest that some of the negative physical-health outcomes associated with abuse (e.g., arthritis, obesity, cardiovascular health) may be associated with developmental exposure to harsh physical punishment, which does not meet severity criteria for maltreatment (Afifi, Mota, MacMillan, & Sareen, 2013). This suggests that some of the effects of early adversity among foster children and others may exist along a continuum of stressors with potential detrimental effects at levels even below *maltreatment* thresholds.

However, recent research findings also suggest multiple biological pathways that are perturbed in adulthood based on childhood maltreatment status. This research includes the effects of child maltreatment and physical health from clinical adult populations that are referred for specific medical problems. It also includes evidence from matched-cohort designs of children with substantiated maltreatment and community controls (Davis, Luecken, & Zautra, 2005; Widom, Czaja, Bentley, & Johnson, 2012).

One prospective study has followed children with a documented adversity history and community controls to adulthood, examining blood, vision, and respiratory biomarkers of health risk and controlling for a number of sociodemographic and lifestyle variables (Widom et al., 2012). This study found increased risk for diabetes (indexed by higher levels of poor glycemic-control blood levels), lung disease (indexed by poor peak airflow), and vision problems (indexed by an acuity test) in adults who experienced early adversity. The race and gender interactions suggested that women were at particular adversity-related risk for poor glycemic control and that White adults were at increased adversity-related risk for heart disease (as indexed by C-reactive protein). Other research on pubertal timing has highlighted the impacts of early adversity on developmental physical processes, with early neglect being associated with slowed pubertal development that later increased in boys; in contrast, sexual abuse was specifically associated with early pubertal timing for girls (Negriff, Blankson, & Trickett, 2014).

A specific focus on the biological bases of pain perception has been studied, given the diverse types of pathological presentations that include chronic pain (e.g., chronic pelvic pain, fibromyalgia, migraines) that are found to be overrepresented in samples with histories of adversity (Arnow, 2004; Davis et al., 2005; Tietjen et al., 2010; Walker et al., 1997; Walker et al., 1988). Evidence and theory suggest that a history of adversity may result in increased vulnerability to experiencing pain through stress-related hormonal processes (Arnow, 2004; Fisher, Gunnar, Dozier, Bruce, & Pears, 2006; Nicolson, Davis, Kruszewski, & Zauta, 2010). Research among adult women with fibromyalgia, a chronic pain condition without a known medical explanation, has shown that self-reported childhood maltreatment is associated with higher diurnal cortisol levels compared with women without maltreatment histories. This suggests that, although the dysregulated HPA-axis functioning may not be a contributing factor to fibromyalgia in all women, it may be a contributor or indicator of fibromyalgia risk in women who have experienced maltreatment.

Genetic Research Related to Adversity

Among the most noteworthy developments in recent years is the discovery of specific genetic vulnerabilities that may be responsible for poorer outcomes among some individuals who have experienced early adversity (Banny, Cicchetti, Rogosch, Oshri, & Crick, 2013; Caspi et al., 2002; Cutuli, Raby, Cicchetti, Englund, & Egeland, 2013). In this research, genetic vulnerabilities often interact with early environmental adversity (GxE interactions) to predict negative outcomes more likely to occur in the presence of early adversity. In the first study to document this effect, Caspi et al. (2002) found that among individuals who had experienced early adversity, carriers of a low activity MAOA-1 allele were at particular risk for antisocial behavior. Follow-up research has shown that this polymorphism is associated with an exaggerated neurocognitive response to threat and reduced activity in the brain regions involved in emotion regulation, suggesting a heightened vulnerability to aggressive or reactive behaviors (McCrory et al., 2012). Other notable studies have focused on Gene x Environment interactions of early adversity that predict later life depression based on polymorphisms of the serotonin transporter gene, which influences the availability of the serotonin neurotransmitter at neuronal synapses (Banny et al., 2013; Cutuli et al., 2013). Additional research has shown that genetic variations relevant to neuroendocrine stress response predict dysregulation of stress-related hormones (e.g., cortisol) in maltreated, but not in nonmaltreated, samples (Cicchetti, Rogosch, & Oshri, 2011).

Additional recent developments in the genetics literature include findings suggesting that early adversity may also affect the expression of specific genes (*epigenetic effects*), thereby modifying the blueprint for ontogeny provided by DNA (Essex et al., 2013). In rodent models, developmental exposure to maltreating caregivers can lead to changes in gene expressions related to neural growth, which is particularly important for prefrontal cortex development (Roth, Lubin, Funk, & Sweatt, 2009). The only study on early adversity to date in humans has shown support for epigenetic effects in adolescents related to maternal stress during the adolescent's infancy and paternal stress when the adolescent was preschool age. The implications of these effects have yet to be established, with some changes occurring in genes with plausible links to family stress (e.g., genes coding for cellular differentiation in the nervous system) and others in genes with no identified links (Essex et al., 2013). Increased cellular aging, as indexed by reduced telomere length, has also been reported among adults with a history of early adversity; however, the mechanisms contributing to increased cellular aging have yet to be established (Tyrka et al., 2010).

Summary

This large body of evidence across research among high-risk populations that include foster and maltreated

children suggests that early adversity contributes to profound changes in healthy biological, brain, and physical development. Recent genetic research findings suggest that certain phenotypes increase a child's vulnerability to the effects of adversity on outcomes such as depression and antisocial behavior. At the neuroendocrine level, early adversity is well documented to contribute to dysregulation of the HPA axis and atypical patterns of cortisol in the body. The effects of dysregulated cortisol production are strongly supported by animal models to contribute to a range of neurocognitive and physical health consequences, which are commonly overrepresented in samples with histories of early adversity. Evidence of atypical cognitive processing from fMRI and ERP methods also supports the findings from the animal literature of increased adversity-related deficits in brain regions with higher densities of glucocorticoid receptors. Given the widespread effects of early adversity on developing bodily systems, it is particularly promising that early intervention has been shown to ameliorate atypical development of neuroendocrine and cognitive-response monitoring processes. Ongoing research in the area is seeking a more in-depth description of the underlying mechanisms, which could advance the ability of interventions to improve outcomes for individuals with histories of early adversity.

THE TIMING AND DURATION OF ADVERSITY IS ASSOCIATED WITH DIFFERENTIAL BEHAVIORAL AND NEUROBIOLOGICAL OUTCOMES, WITH A GENERAL TREND OF LONGER LASTING ADVERSITY PRODUCING THE MOST PROFOUND EFFECTS

Although the animal literature contains extensive information about the timing and duration of effects of adversity on typical development, research with humans is much less suited for characterizing how such dimensions of adversity lead to alterations in key domains of functioning. However, research on foster care provides some information in this area. Consistent with findings from the institutional-rearing and international-adoption literatures, research findings about foster children indicate that increased time spent in adversity increases the likelihood for compromised outcomes. For example, children in the previously described NSCAW sample who lived in maltreating families longer (placed in foster care at older ages) showed more behavior problems than did those placed in care at younger ages (Burns et al., 2004). Perhaps what is most noteworthy about these results is that the effects of prolonged exposure to adversity appear to outweigh the effects of out-of-home placement. Other research on symptoms of serious psychopathology, such as borderline personality disorder, also suggests that the chronicity of adversity is particularly predictive of negative outcomes (Hecht, Cicchetti, Rogosch, & Crick, 2014). Moreover, research with a large cohort of public-school children has shown that earlier onset adversity is linked to increased academic problems (Fantuzzo, Pearlman, & Dobbins, 2011).

Although evidence across studies shows that the chronicity and earlier onset of adversity are related to more severe behavioral problems, research findings also suggest that the timing of certain types of maltreatment predicts distinct behavior problem trajectories (Keiley, Howe, Dodge, Bates, & Pettit, 2001; Manly, Kim, Rogosch, & Cicchetti, 2001). In particular, the severity of physical neglect in infancy has been related to later developing externalizing behavioral problems, whereas the severity of physical neglect in the preschool years has been related to later developing internalizing problems. In this same study, emotional abuse in infancy and physical abuse in the preschool years were related to externalizing problems. It is important to note that maltreatment in the school years contributed significant variance to behavioral problems after controlling for earlier maltreatment, suggesting that although earlier onset maltreatment might be the most harmful, later maltreatment also contributes to significant behavioral problems (Keiley et al., 2001). In growth models of behavioral problems, children who experienced later onset maltreatment have been shown to exhibit a more rapid increase in externalizing behavior despite having fewer behavioral problems at kindergarten entry.

Supportive evidence about the importance of the timing and duration of adversity can be derived from international studies such as The English and Romanian Adoptee (ERA) Project. The ERA Project investigated the development of Romanian children adopted into the United Kingdom in the early 1990s. The vast majority of the adoptees had experienced extreme early global deprivation up to age 42 months as a consequence of their early placement in Romanian institutions (Rutter et al., 2010). However, there was greater catch-up among children who were adopted prior to age 6 months (Rutter et al., 2010). Overall, the research in this area corroborates evidence from the animal literature and highlights the vulnerability of children to early and prolonged adversity.

In addition to the behavioral consequences associated with a longer duration of adversity, exaggerated adversity-related effects on brain development have been documented. Specifically, in a study of children with

maltreatment and PTSD, researchers found that smaller brain volume was associated with a longer duration of maltreatment and an earlier onset of PTSD-related trauma (DeBellis et al., 2002).

Relatively little research has been conducted about the effects of the timing of adversity on brain development, but findings from neuroimaging studies suggest that timing may be important given the differential development of specific brain regions across childhood (Pechtel & Pizzagalli, 2011). For example, in young adult females who experienced childhood sexual abuse, the abuse has been shown to predict different impacts on regional brain volume associated with timing of exposure (Andersen et al., 2008). Sexual abuse in very young children (ages 3–5 years) and early adolescence (ages 11–13 years) was shown to be associated with smaller hippocampal volume, whereas abuse in other age groups was shown to be associated with reduced volume in the corpus callosum (ages 9–10 years) and the prefrontal cortex (ages 11–13 years). Such changes are theorized to reflect the fact that brain regions may be differentially developing at distinct time points and, accordingly, may be differentially vulnerable based on the timing of maltreatment. However, as noted by Pechtel and Pizzagalli (2011), the specific mechanisms underlying such time-sensitive structural abnormalities have been minimally described despite extant theory related to the role of neurogenesis, myelination, and synaptic pruning.

The importance of timing has also been highlighted in a study investigating maltreatment-related declines in brain volume of the amygdala, thalamus, and caudate (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). In early adulthood, participants (maltreated and control) were asked to recall specific maltreatment periods in their childhood to understand the importance of timing and severity on brain volume. Although the thalamus and caudate volumes were not different in the maltreated group, right amygdala volume was significantly larger in individuals who experienced childhood maltreatment, with larger volume associated with increased severity of maltreatment. Furthermore, a sensitive preadolescent period (ages 10–11 years) with even moderate maltreatment exposure contributed to increased right amygdala volume. The authors noted that the right (vs. left) amygdala exhibits a prolonged developmental trajectory and has been shown to be particularly sensitive to maternal prenatal stress (Pechtel et al., 2014). Furthermore, multiple fMRI studies have demonstrated maltreatment associated hyperreactivity of the amygdala to emotional stimuli (Dannlowski et al., 2012; van Harmelen et al., 2013). Based on animal studies, researchers have highlighted the potential significance of the preadolescent/prepuberty period for its increased neural pruning, but the mechanisms contributing to such a sensitive period are unknown (Pechtel et al., 2014).

Taken together, these results strongly suggest that the duration and severity of maltreatment are associated with increased aberrations from typical development. Theory suggests the potential importance of timing on different outcomes associated with the changing developmental processes of the body and brain (Pechtel & Pizzaglli, 2011). However, the evidence for such impacts in humans is just emerging. Multiple methodological challenges must be overcome to examine and understand the impacts of timing, including recruitment of sufficient sample sizes of at-risk children and the potential for regionally specific effects, which require the development of specific hypotheses to detect potential differences (Teicher & Samson, 2013).

NEGLECT IS A PARTICULAR CAUSE FOR CONCERN BECAUSE OF ITS PERVASIVENESS AND ITS PROPENSITY TO DISRUPT HEALTHY DEVELOPMENT AND EXERT A LASTING IMPACT ON HEALTH AND WELL-BEING

One of the lesser known characteristics of the foster care population, but one that has been the focus of research and public policy in recent years, is that many children are placed in out-of-home care because of neglect (e.g., failure to provide age-appropriate care, food, shelter, healthcare, supervision, or safety precautions) rather than physical and sexual abuse. Neglect is nearly ubiquitous among foster children—for example, more than 78% of foster children are estimated to be in care because of neglect alone, and nearly all those in care because of abuse have experienced neglect (U.S. Department of Health and Human Services, 2012). Moreover, neglect—even in the absence of other maltreatment—appears to represent a serious threat to the health and well-being of young children.

Neglect is an interesting phenomenon from a developmental perspective because it represents an omission of expected caregiving input rather than a commission of an act of physical or sexual violence toward the child. Because neglect is not an overt form of abuse and leaves no physical marks, the damage resulting from prolonged neglect may be more difficult to detect. However, as reviewed later, there is increasing evidence that neglect represents a threat to mental and physical development, which may become apparent in later years as the child experiences delays and is unable to keep pace with peers on key tasks of cognitive,

physical, or socioemotional development. The difficulty detecting neglect, especially among infants and toddlers who lack the language to describe their experiences, is one of neglect's most concerning qualities.

It is important to qualify any discussion of neglect by noting that neglect does not occur when a parent is unresponsive intermittently but otherwise consistent in providing care and promoting a loving environment. Intermittent inattentiveness is not cause for concern; rather, it may have the potential to promote independence in the child and increase the child's ability to self-soothe and problem solve. Similarly, variability in the attention given to the child by the parent has been shown to benefit the child. Such variability in an otherwise nurturing environment represents positive stress that has been shown to be beneficial to children as young as age 6 months (Tronick & Gianino, 1986).

One way to understand why neglect is so impactful is to consider the importance of adult–child interaction in development. Development in childhood is hierarchical in nature. Early skills develop out of consistent and nurturing interactions with caregivers, and these skills lead to later success and aptitude in academics, physical achievement, and control of the surrounding social environment (Shonkoff, Garner, et al., 2012). Neglect essentially represents the absence of evolutionarily expected environmental input.

Much of the research on the effects of neglect has not been specific to foster care; however, when compared with the general population, neglected children are clearly overrepresented in foster care. Moreover, neglect samples often contain many children currently in care or with a history of child welfare involvement. Research on samples of neglected children has consistently found that neglect is associated with numerous effects on development, health, and well-being (Horwitz, Widom, McLaughlin, & White, 2001). For example, the longitudinal Minnesota Mother–Child Project examined 267 children born to mothers who, for various reasons, were at risk for neglectful or psychologically reserved parenting, that is, *psychologically unavailable* mothers and *neglectful* mothers who failed to provide physical care and protection to their child. When these two groups of mothers were compared with other maltreatment groups, the neglected children performed the worst on the Bayley Scales of Infant Development from 9 to 24 months of age (Egeland & Sroufe, 1981; Hildyard & Wolfe, 2002). The neglected children also possessed more behavioral problems, including frustration and anger in problem solving. At age 48 months, the neglected children showed poor impulse control on an obstacle task and showed less creativity in problem solving. Neglected children's academic and cognitive abilities suffered as well (Gowen, Christy, & Sparling, 1993).

DeBellis et al. (2009) investigated the academic performance of neglected children and that of their nonneglected peers. The neglected children performed significantly lower on measures of intelligence. In addition, neglected children lacked aptitude in tasks that measure memory for faces, names, and narratives. Egeland and Sroufe (1981) examined the attachment behavior of 31 maltreated children and 33 nonmaltreated children, based on attachment theory. During feeding and play, all the children of mothers who lacked the basic skills in caring for their child were anxiously attached and in the avoidant attachment group at age 12 months. The authors further noted that following DHS intervention to remove the child from the home for some period of time, the mother was totally psychologically unavailable. Rutter et al. (2010) noted the co-occurrence of many symptoms of neglect and identified a specific behavioral phenotype among children who had experienced institutional deprivation (a severe form of neglect neglect) that included symptoms of quasi-autism, disinhibited attachment, cognitive impairment, and inattention/overactivity.

In institutional settings, neglect can be especially extreme (a condition referred to as *privation*). According to UNICEF, an estimated 1.5 million children in Central and Eastern Europe live in public care institutions, where it is typical for children to outnumber caregivers 15 to 1. In many contexts, caregivers work 8-hour shifts, meaning that the limited contact the child receives is provided by a changing "cast of characters." Research on children reared in institutional settings provides evidence that neglect affects neurobiological development. For example, Tottenham et al. (2010) examined the whole brain and limbic structures (amygdala and hippocampus) of children adopted following early institutional care versus a healthy comparison group. Measures used included indicators of emotion regulation, anxiety, and internalizing behavior. Results indicated that the later a child was adopted, the more psychiatric disturbances were associated with larger amygdala volumes, poorer emotion regulation, and increased anxiety.

The ability to recover from neglect varies depending on the specific experiences of the child and on genetic factors. The environment that the child enters after being exposed to neglectful conditions can benefit or hinder such recovery. The more stimulating the home and the more supportive the caregivers are, the better the child's chance to catch up with peers (Bradley & Caldwell, 1984). Foster care, when paired with supportive parenting programs,

offers a first step for promoting learning and development in neglected children.

TRANSITIONS AMONG PRIMARY CAREGIVERS ARE A SPECIFIC CLASS OF ADVERSE EXPERIENCE WORTHY OF ATTENTION BECAUSE THEY APPEAR TO NEGATIVELY AFFECT THE DEVELOPMENT OF KEY COGNITIVE AND BEHAVIORAL SKILLS NEEDED FOR SOCIAL AND ACADEMIC SUCCESS

Although the child–caregiver attachment system has been investigated extensively in the literature, it is most often assessed within the context of the child's relationship with permanent primary caregivers (e.g., biological or adoptive parents). In contrast, foster care research uniquely allows us to examine the pliability of the attachment system in children across multiple caregiver relationships. Indeed, within the context of foster care, transitions between caregivers are common: one to two thirds of foster placements disrupt within 12–24 months of placement, for various reasons (Wulczyn, Hislop, & Chen, 2007). In addition to uncontrollable child problem behavior, other variables appear to cause placement failures. In a study about this topic, Oosterman, Schuengel, Slot, Bullens, and Doreleijers (2007) conducted a meta-analysis of research involving more than 20,000 foster children. In addition to child problem behavior, the strongest predictors of placement failure were older age at placement, history of residential treatment, and number of prior placements. Similarly, Fisher, Burraston, and Pears (2005) found that placement instability essentially begets further instability. Placement transitions in foster care also result from administrative decisions (e.g., siblings subsequently being removed from the birth parents and placed into care). Moreover, even positive changes, such as reunification with birth parents or adoption, represent caregiver transitions.

Regardless of the cause, caregiver transitions appear to have the potential to compromise typical development. Rubin, O'Reilly, Luan, and Localio (2007) examined placement instability among NSCAW children and categorized the children according to whether or not they achieved a stable placement within 18 months in out-of-home care. They found that more than one quarter of the sample failed to achieve a stable placement and that placement instability predicted problem behavior, as assessed using the Child Behavior Checklist. Specifically, placement instability resulted in a 63% increase in problem behavior. In a second study, Chamberlain et al. (2006) found that the number of behavior problems was directly related to the number of placement disruptions.

Placement disruptions have also been shown to contribute to foster child inhibitory-control difficulties. Pears, Bruce, Fisher, and Kim (2010) reported that among a sample of foster preschoolers, the number of unique placements a child had experienced was significantly correlated with inhibitory control problems. These inhibitory control problems were noted as being part of a more general set of difficulties with self-regulation that included indiscriminate friendliness. Similarly, Lewis, Dozier, Ackerman, and Sepulveda-Kozakowski (2007) examined inhibitory control in a sample of foster children who were adopted following care, including children with and without a history of placement instability. They found that the children with a history of placement instability (vs. that of the comparison group) performed more poorly on a measure of inhibitory control derived from a day/night Stroop task and were rated as more oppositional (although inhibitory control did not mediate the association between placement instability and oppositional behavior).

To summarize, research on foster children provides evidence that experiencing caregiver transitions has the potential to disrupt healthy child development. In particular, the literature suggests that such transitions are associated with an increased likelihood for disruptive behavior and inhibitory-control difficulties. These findings provide evidence that this particular form of adversity may interfere with the development of regions of the prefrontal cortex involved in executive functioning, suggesting that policy and programming designed to mitigate risks for foster children (and others) should seek to prevent or reduce the number of caregiver transitions that children experience.

THE COMBINED EFFECTS OF PRENATAL STRESS (ESPECIALLY PRENATAL SUBSTANCE EXPOSURE) AND EARLY ADVERSITY ON NEUROBEHAVIORAL DEVELOPMENT ARE ADDITIVE AND PRODUCE WORSE OUTCOMES THAN PRENATAL STRESS OR EARLY ADVERSITY ALONE

Although research on foster children and other samples experiencing early neglect/deprivation provides a strong case for the cumulative effects of adversity on typical development, one noteworthy aspect of this evidence base is that it focuses almost exclusively on experiences that occur after the birth of the child. In reality, for many

foster children, adversity begins at conception, continues throughout pregnancy, and is ongoing antenatally. An extensive literature involving animal models and humans documents the effects of prenatal adversity (particularly substance use) on biobehavioral development (Thompson, Levitt, & Stanwood, 2009). However, to be consistent with the natural ecology of foster children (and many other high-risk populations), modeling *the combined effects of prenatal and early adversity* is a necessary addition to examining separately the effects of either developmental period. Interestingly, relatively limited research has been conducted in this area.

Foster Care as a Context for Prenatal Substance Exposure

Foster care provides an excellent context for examining the combined effects of prenatal substance exposure and early adversity. Estimates are that between 43% and 79% of the parents of foster children meet criteria for a substance use disorder (Besinger, Garland, Litrownik, & Landsverk, 1999; Young, Boles, & Otero, 2007). Also, 80% to 90% of cases of neglect reported to child welfare involve parental substance use disorder (Dunn et al., 2002). Thus, it is likely that for many foster children, parental substance use occurred at least intermittently if not throughout pregnancy. Indeed, evidence for this exists in the literature. For example, in a study of 204 infants placed in family foster care at ages 0–15 months, prenatal substance exposure was verified for 61.7% and suspected for 16.7% of the infants (McNichol, 1999). Similarly, in a foster care population in Washington state, the rate of fetal alcohol syndrome was 10–15 times greater than in the general population (Astley, Stachowiak, Clarren, & Clausen, 2002).

In response to the recognized prevalence rates of prenatal substance exposure and the risks associated with such exposure, 19 states and the District of Columbia have implemented mandatory reporting procedures at birth for prenatally exposed infants, and 12 states and the District of Columbia define *prenatal exposure* as child abuse or neglect (Child Welfare Information Gateway, 2011). Perhaps owing to the vigilant use of these indicators of prenatal exposure at the birth of a child, these infants are some of the youngest foster children. For example, McNichol (1999) found that infants with verified prenatal substance exposure (verified by maternal self-report or toxicology tests at birth) were placed in foster care at a significantly earlier mean age (3.8 months) than were infants with suspected prenatal exposure (5.6 months) and infants with no suspected exposure (5.9 months). Further, nearly half of the prenatally exposed infants were placed in care within 1 month of birth. Similarly, in a study of high-risk mother–infant dyads recruited at birth, Eiden, Foote, and Schuetze (2007) found that 19.1% of the infants prenatally exposed to cocaine entered foster care within 1–2 months of birth. Prenatally exposed infants are also likely to be exposed to postnatal parental substance use and its attendant risk for neglect (Dunn et al., 2002) and primary caregiver transitions (Bauer et al., 2011). They also have a high propensity to be placed in foster care, where they often experience further placement transitions (Smith, Johnson, Pears, Fisher, & DeGarmo, 2007).

Methodological Challenges to Research on Prenatal Substance Exposure

Before considering the combined influences of prenatal and early adversity on foster children, we briefly review prenatal substance exposure and its major short- and long-term effects. The majority of research on prenatal exposure has considered the effects of alcohol, tobacco, cocaine, methamphetamine, marijuana, and opiates on the developing fetus. Epidemiological evidence suggests that alcohol (10%) and tobacco (16.7%) are the most common substances consumed by pregnant women (Substance Abuse and Mental Health Services Administration, 2009). There are a number of challenges to definitively predicting the impact of prenatal exposure on infant outcomes. First, the quantity, frequency, and timing of prenatal substance use vary across women, and drug effects on fetal development vary by stage of gestation, with more significant teratogenic effects being observed during the embryonic stage (particularly in the case of alcohol) and more subtle effects being observed during the fetal period (Behnke, Smith, Committee on Substance Abuse, & Committee on Fetus and Newborn, 2013). Moreover, some pregnant women eliminate substance use when they learn of their pregnancy, (although this may not occur until well into the pregnancy, whereas others never desist from substance use [Massey et al., 2011]). Rates of prenatal substance use also vary by age group, with past-month alcohol and illicit drug use levels being higher for pregnant teenagers ages 15–17 years, compared with adults ages 18–25 years (Substance Abuse and Mental Health Services Administration, n.d.).

Efforts to disentangle the effects of prenatal substance exposure on biobehavioral development are complicated by a number of issues. First, the reality is that most prenatal substance exposure involves multiple substances (Lester, Andreozzi, & Appiah, 2004). In spite of the fact that the literature reports many studies that are designed to investigate the effects of a specific substance (e.g., alcohol,

cocaine) on the fetus, a great many of the individuals in the samples that have been gathered are polysubstance exposed. There are advantages and disadvantages of this methodological strategy. On the positive side, polysubstance exposure appears to be something of a reality for many women who use alcohol, tobacco, and illicit drugs during pregnancy. Moreover, some studies have attempted to control for the effects of substances that are not the focus of the investigation by using statistical covariation. Nevertheless, it is not clear that the extant knowledge base involving humans provides a clear picture of the effects of specific substances on development.

Although it is difficult to find nationally representative statistics for polysubstance exposure, several studies highlight this phenomenon as it manifests in high-risk and child welfare–involved families. In the Infant Development, Environment, and Lifestyle (IDEAL) longitudinal study of prenatal methamphetamine exposure, women who used methamphetamine (vs. those who did not) consumed significantly more tobacco (71% vs. 25%), alcohol (49% vs. 16%), and cannabis (43% vs. 8%) during pregnancy (Derauf et al., 2007). Among women referred to a perinatal addiction outpatient clinic in the United Kingdom, 49% were polysubstance users of at least two of the following drugs: heroin, cocaine, alcohol, cannabis, and methamphetamine (Mayet, Groshkova, Morgan, MacCormack, & Strang, 2008). In a study of a 3-year home visitation intervention for mothers with alcohol or other drug problems during pregnancy ($N = 458$), the women used tobacco (90%), alcohol (73%), cocaine (63%), cannabis (63%), and methamphetamine (42%; Grant et al., 2011). Despite the prevalence of prenatal polysubstance exposure, the mechanisms by which multiple substances interact to influence fetal development are not yet understood (Lester et al., 2004).

A related issue that complicates research in this area is that prenatal substance exposure is likely to co-occur with many other known stressors. For example, prenatal nutrition may be inadequate for many of these infants. Poverty, domestic violence or other relationship stress, and other environmental stressors may also be present. These variables may represent confounds in the assessment of prenatal exposure.

Developmental Outcomes of Prenatal Substance Exposure

In spite of the limitations in the research methodology, research on prenatal exposure has yielded a considerable amount of important information. In general, the adverse effects of prenatal substance use are attributed to alterations in the development of the fetal brain and autonomic nervous system. This is a logical supposition, inasmuch as substances used by the mother cross the placenta, where they may exert specific or individual effects (Behnke et al., 2013; Lester et al. 2004). In their model of the developmental effects of prenatal substance exposure, Lester and colleagues (2004) proposed that immediate drug effects emerge in early infancy (before the postnatal environment becomes influential) and may be transient or long lasting. For instance, tobacco use has twice the impact on infant birth weight compared with illicit drug use (Bailey, McCook, Hodge, & McGrady, 2012). However, by age 24 months, few studies find effects of fetal tobacco exposure on physical growth (Behnke et al., 2013). As an example of a longer lasting immediate drug effect among prenatally exposed (cocaine) children, high neonatal arousal and stress (an immediate drug effect on neonatal neurobehavior) have been indirectly associated with increased problem behavior at ages 3 and 7 years via difficult temperament at age 4 months (Lester et al., 2009).

Lester and colleagues (2004) argued that in addition to immediate drug effects, latent drug effects can be observed later in development in the context of brain and behavior effects specific to older children. For instance, a recent meta-analysis revealed a significant association between any binge alcohol exposure (≥ 4 or ≥ 5 drinks per occasion) during pregnancy and negative child cognition outcomes between ages 6 months and 14 years (Flak et al., 2014). These researchers also observed a significant, detrimental association between moderate prenatal alcohol exposure ("up to 6 drinks per week, including some individuals who consumed at least 3 drinks per week," p. 215) and child behavior between ages 9 months and 5 years. During the transition to adolescence, prenatally exposed youths demonstrate an especially pronounced vulnerability to substance use. For example, in a prospective longitudinal study, Cornelius, Goldschmidt, and Day (2012) found that prenatal exposure to cigarette smoking at all three trimesters predicted earlier child smoking experimentation at age 10, heavier smoking at age 14, and higher rates of smoking and addiction to nicotine at age 22, all while accounting for prenatal exposure to other drugs. Parallel outcomes have been observed among adolescents prenatally exposed to alcohol (Behnke et al., 2013).

Developmental Outcomes of Prenatal Exposure Among Children With Foster Care Histories

Prenatally exposed foster children tend to demonstrate more latent drug effects than do their prenatally exposed

peers in stable living arrangements, suggesting that prenatal effects are compounded by subsequent experiences. For example, in a prospective longitudinal study from birth, prenatally exposed 6-year-olds (n = 169) self-reported more symptoms of oppositional defiant disorder and ADHD than did nonexposed children (n = 153; Linares Singer et al., 2006). Further, prenatally exposed children in adoptive or foster care (n = 36) self-reported significantly more externalizing symptoms than did nonexposed children (n = 153) and prenatally exposed children living in maternal or relative care (n = 133; Linares Singer et al., 2006). Notably, the sample in the studies by Linares and colleagues was specifically selected for prenatal cocaine exposure.

Several prospective longitudinal studies from birth have followed prenatally exposed children with a foster care history into adolescence. In one study of prenatally exposed versus nonexposed adopted children (some adopted from foster care and others from private agencies or other means), the prenatally exposed adolescents exhibited significantly more externalizing problem behavior, according to parent reports 14 years postadoption (Crea, Barth, Guo, & Brooks, 2008). In another prospective longitudinal study, pregnant women considered to be at risk for prenatal substance use were recruited at the child's birth (Min, Minnes, Yoon, Short, & Singer, 2014). Behavioral adjustment at ages 12 and 15 years was compared between subsamples of prenatally exposed (cocaine) and nonexposed youths. Controlling for covariates, including prenatal exposure to alcohol, tobacco, and cannabis, prenatal exposure was associated with more externalizing behavior problems at ages 12 and 15 years and with more attention problems at age 15 years. Consistent with findings from Linares et al. (2006), the prenatally exposed adolescents in nonkinship foster or adoptive care (23% of the prenatally exposed adolescents) reported significantly more externalizing and attention problems than did nonexposed adolescents in nonkinship foster or adoptive care (4.5% of the nonexposed adolescents) at ages 12 and 15 years (Min et al., 2014).

Behavioral maladjustment in prenatally exposed (cocaine) adolescents in nonkinship foster or adoptive care occurred despite these caregivers having higher educational attainment and less substance use than biological/relative caregivers of prenatally exposed youths had (Min et al., 2014). There are several possible explanations for this finding. In keeping with the developmental model proposed by Lester and colleagues (2004), the heightened behavioral maladjustment of prenatally exposed (cocaine) adolescents in foster or adoptive care could reflect latent effects of prenatal cocaine exposure on fetal nervous-system development. In addition, prenatally exposed youth may have endured more severe or persistent early adversity than did their nonexposed peers. This heightened early adversity, in turn, may have contributed to their entry into foster care and to their long-term biobehavioral development. Taken together, the findings from these studies of children with foster care histories illustrate the importance of understanding the effects of prenatal substance exposure in the context of the child's early caregiving environment.

The Combined Effects of Prenatal Substance Exposure and Early Adversity

Beyond understanding the immediate and latent effects of specific drugs, it is important to identify risk and protective factors in the postnatal caregiving environment that moderate prenatally exposed children's developmental outcomes (Lester et al., 2004). Research on the combined effects of prenatal and early adversity is in its early stages. Commonly, studies that account for the postnatal environment in their analyses have conceptualized the environment as a variable that must be controlled to isolate the independent effects of prenatal exposure to a specific substance. These studies are frequently motivated by behavioral-teratology questions. However, a few studies have considered the independent, mediated, and moderated effects of prenatal exposure and early adversity on developmental outcomes from infancy into adolescence. Research findings about aspects of the postnatal environment that mitigate prenatal-exposure effects on child outcomes suggest important directions for future research and prevention in this area. In the remainder of this section, we provide a representative summary of existing evidence about the combined effects of prenatal exposure and early adversity in samples of children recruited on the basis of prenatal exposure—some that included children with histories of foster care and some that focus exclusively on foster children.

Independent Effects of Prenatal Exposure and Early Adversity

Lambert et al. (2013) examined the effects of prenatal exposure and other demographic and environmental risk factors on risk-taking behavior among 963 adolescents in the Maternal Lifestyle Study, a multisite, longitudinal cohort study that examined prenatal exposure effects in a sample that included 433 prenatally exposed (cocaine) infants and 530 nonexposed infants. Children in this landmark study, many of whom had contact with the child

welfare system or a history of placement in foster care, have been followed from birth through the transition to adulthood, with multiple waves of data collection. The assessment includes developmental and behavioral indicators of adjustment and measures of neurobiological functioning. Analyses of this data set have revealed that prenatal cocaine exposure, caregiver socioeconomic status (SES), and male child gender predicted increased odds of being arrested by age 15 years. In contrast, prenatal exposure to cocaine, alcohol, tobacco, or cannabis did not predict increased odds of adolescent alcohol, tobacco, or marijuana use. Rather, other demographic or environmental variables, such as having friends who used each drug, predicted adolescent substance use behaviors. For instance, caregiver abuse, number of caregiver changes, and having friends who used alcohol predicted increased odds of alcohol use at age 15 years. In the case of sexual risk-taking behavior at age 15 years, only prenatal exposure to cocaine or cannabis was predictive. Taken together, community violence, low parental involvement, male child gender, and other postnatal demographic and environmental factors contributed more to the prediction of sexual risk-taking behavior than did prenatal exposure (Lambert et al., 2013). Using data from the same study, Conradt et al. (2014) found that prenatal polysubstance exposure and early adversity did not relate to physiological correlates of behavioral and emotional problems in early childhood or adolescence. However, prenatal polysubstance exposure and early adversity related (differently for males and females) to neurobehavioral outcomes at age 13 years that were associated with risk-taking behavior at age 16 years.

Additional information about the combined effects of prenatal substance exposure and early adversity—specifically among foster children—can be derived from a Norwegian study. This prospective, longitudinal investigation of children prenatally exposed to opiates and other substances examined the effects of prenatal exposure on cognitive development at age 4.5 years (Moe, 2002). The sample for this study was considerably smaller than that of the aforementioned study by Lester and colleagues (2009). It consisted of 64 children who were prenatally exposed and 58 in the comparison group. Of the prenatally exposed group, 79.7% were diagnosed with a neonatal abstinence syndrome (i.e., withdrawal) and 84.6% were placed in foster care during infancy. The foster caregivers were recruited specially to provide care for at-risk infants, enabling the researchers to examine the effects of prenatal exposure under conditions of minimal postnatal risk. There was a significant interaction between male child gender and prenatal substance exposure such that boys in the prenatal-exposure group demonstrated the lowest general cognitive ability and the lowest perceptual, memory, and motor scores on the McCarthy Scales of General Ability. For the whole sample, prenatal exposure, foster-caregiver SES, gestational age, and mental development at age 1 year were independently associated with lower perceptual performance at age 4.5 years. However, prenatal exposure was not associated with general cognitive ability when these postnatal predictors were added to the model. Rather, only parental SES and mental development at age 1 year predicted general cognitive ability scores. It appears that, especially for girls, specialized foster care may have been protective of the effects of prenatal exposure on general cognitive ability. However, more research on larger samples is necessary to adequately understand the gender effects that were observed.

Early Adversity as a Mediator of the Effects of Prenatal Substance Exposure

In addition to the previously described work that has examined the separate effects of prenatal exposure and early adversity, several studies have examined early adversity as a mediator of the association between prenatal exposure and neurobehavioral disinhibition in childhood and adolescence. Mediation assumes that the developmental consequences of prenatal exposure are partly explained by the adverse postnatal conditions typically associated with maternal substance use during pregnancy. In two studies on this subject (Abar et al., 2012; Fisher et al., 2011), early adversity was assessed as a summative risk index that measures the presence of postnatal parental substance use, chronic poverty, primary caregiver changes, community violence, sexual/physical abuse, and other risk factors.

Using data from the Maternal Lifestyle Study, Fisher et al. (2011) examined the emergence and growth of a phenotype termed *neurobehavioral disinhibition* across the transition to adolescence among prenatally polysubstance-exposed youths who experienced early adversity. The neurobehavioral disinhibition construct included a composite measure of behavioral dysregulation and a composite measure of executive-function difficulties. They found that behavioral dysregulation at age 8/9 years predicted growth in executive function difficulties from age 8/9 years to age 13/14 years. Prenatal polysubstance exposure predicted the onset and growth of neurobehavioral disinhibition across adolescence. In the case of behavioral dysregulation, prenatal exposure directly predicted growth of neurobehavioral disinhibition across

adolescence. In the case of executive function difficulties, prenatal exposure was indirectly related to growth in these difficulties through early adversity. Specifically, prenatal polysubstance exposure was related to early adversity, early adversity was related to behavioral dysregulation at age 8/9 years, and behavioral dysregulation at age 8/9 years was related to growth in executive function difficulties across the transition to adolescence. Fisher et al. noted that prenatally exposed youths who enter adolescence with behavior problems may be particularly likely to experience executive function difficulties.

Abar et al. (2012) obtained similar findings among younger prenatally exposed children in the Infant Development, Environment, and Lifestyle study of prenatal methamphetamine exposure. In this study, prenatal methamphetamine exposure was indirectly associated with behavioral/emotional control problems at age 5 years and executive function deficits at age 6.5 years through early adversity experienced from birth to age 3 years. That is, children prenatally exposed to methamphetamine were likely to be exposed to early adversity, which was then associated with increases in behavioral/emotional control problems and executive function deficits. Prenatal exposure was not related to these neurobehavioral outcomes when early adversity was included in the model.

Postnatal Risk and Protective Factors That Moderate the Effects of Prenatal Substance Exposure

Among samples recruited on the basis of prenatal exposure, converging evidence suggests that postnatal family and community adversity can exacerbate the association between prenatal exposure and child outcomes. For example, a study by Lester et al. (2010) found that, at age 11 years, adolescents prenatally exposed to cocaine demonstrated lower elevations in cortisol in response to a laboratory stressor, controlling for prenatal and postnatal drug exposures. Exposure to parental domestic violence between ages 1 month and 11 years also predicted blunted cortisol reactivity to stress. In addition, domestic violence exposure acted as a moderator: Children prenatally exposed to cocaine who also witnessed parental domestic violence were more likely to exhibit blunted cortisol reactivity than were nonexposed children who witnessed domestic violence.

This finding was replicated in a study by Fisher, Kim, Bruce, and Pears (2012): among foster children with prenatal substance exposure, those who had experienced more maltreatment showed significantly lower cortisol elevations in response to a laboratory stressor. Together, these findings suggest that the vulnerability of the HPA axis to environmental adversity may begin during the fetal period and extend through early childhood.

In addition to neuroendocrine effects, there is evidence that combined prenatal and early adversity affect behavioral adjustment. For example, Bada et al. (2012) examined growth in behavior problems from ages 5 to 15 years among prenatally exposed (cocaine or opiate) youths in the Maternal Lifestyle Study. They also evaluated child, family, and community risk and protective factors that could moderate the effects of prenatal exposure on growth in child problem behavior across childhood and into adolescence. The risk factors included caregiver psychopathology, child abuse, male child gender, and postnatal exposure; the protective factors included caregiver involvement, family resources, and child resilience. The number of risk factors (total = 13) and protective factors (total = 9) were summed to create risk and protective indices, respectively. In addition to assessing the impact of risk and protective factors scored in this cumulative way, Bada et al. examined the combination of levels (high vs. low) of risk and protective indices. At child age 5 years, prenatal exposure (vs. nonexposure) was associated with increased externalizing problem behavior. Important to note, a high-risk index combined with a low-protective index contributed to the already-significant effects of prenatal exposure on behavior problems. In addition, among the prenatally exposed children, who had significantly higher total behavior problems at age 5 years, high or low risk in the presence of a high-protective versus low-protective index contributed to greater declines in total behavior problems throughout the study period.

Similarly, in a small sample of 38 children younger than age 16 years who were placed in foster care because of prenatal alcohol exposure, Koponen, Kalland, and Autti-Rämö (2009) examined the role of the caregiving environment in child behavioral outcomes. In this investigation, 82% of children were prenatally exposed to alcohol only; the other children were exposed to other drugs as well. The majority of the children in the sample met diagnostic criteria for fetal alcohol syndrome (58%) or fetal alcohol effects (24%). Compared with children exposed to fewer traumatic experiences as reported by social workers and foster caregivers, the children exposed to three or more traumatic experiences demonstrated more attentional and emotional problems. Conversely, entry into foster care before age 3 years appeared to be a protective factor in that fewer of these children demonstrated attentional and emotional problems than did the children placed at later ages. Age at entry into foster care and number of traumatic experiences were strongly correlated ($r = 0.67$), suggesting

that early entry into foster care protects children from experiencing further traumatic events in the family of origin. The protective effect of conventional foster care is particularly noteworthy, given that the foster caregivers in this sample reported problems of their own during the child's placement (e.g., economic problems = 37%, family violence = 11%). Although it is not possible from this study to determine the extent to which aspects of foster care were protective of prenatal exposure effects, per se, it is clear from these findings that the postnatal environment is an important contributor to behavioral outcomes among children with a history of foster care resulting from prenatal exposure.

Additional, albeit preliminary, evidence that a positive early environment can offset the adverse effects of prenatal exposure can be found in a nonexperimental study of 22 prenatally exposed infants in a specialized early foster care program (D'Angiulli & Sullivan, 2010). The Safe Babies Program was designed to provide foster caregivers with education and support in caring for prenatally exposed infants. The program recruited "experienced and highly qualified foster parents," including "people with relevant professional qualifications in social work, pediatric medicine, and nursing in addition to their experience as foster parents" (p. 461). Infants for whom parental substance use during pregnancy was the main factor for court-ordered foster care were placed in care before age 24 months. The authors compared the developmental outcomes, including basal salivary cortisol, between full-term and preterm infants enrolled in the program. Compared with full-term infants, preterm infants were in the norm on all developmental domains (assessed with the Battelle Developmental Inventory) except fine motor skills. The preterm and full-term foster infants scored within two standard deviations of the mean on all developmental domains, suggesting no developmental delays. The infants' circadian cortisol rhythms were consistent with typical infant patterns and did not differ between preterm and full-term infants when number of months in foster care was included as a covariate in the analysis. It is important to acknowledge the limitations in this study from a methodological perspective. Confidence in the interpretation of these findings will be increased with the inclusion of a comparison group that does not receive the specialized foster care intervention.

Although the knowledge base in this area is still emerging, the body of research presented here suggests important opportunities for prevention and intervention scientists working with foster families. Although postnatal interventions would not necessarily protect prenatally exposed infants from the immediate neurobehavioral effects of prenatal exposure at birth, such interventions could help mitigate the long-term, or latent, effects of prenatal exposure. Interventions that support and enhance the caregiving capacity of foster caregivers will be particularly relevant in this regard (Healey, Fisher, van Scoyoc, & Relling, 2013). Many important questions remain, the answers to which will help refine existing intervention strategies. For example, it is not clear which dimensions of early adversity are the most detrimental and the most protective of child outcomes among prenatally exposed children. It is also uncertain how the timing of exposure to prenatal and postnatal adversity contributes to child outcomes. Finally, although the general rule is that earlier is better for intervention to offset the effects of postnatal adversity, more research is needed to determine how early in the child's development postnatal protective influences are needed to positively affect outcomes.

In sum, research on foster children and other prenatally exposed populations provides evidence that prenatal adversity represents an independent set of influences over and above the risks conferred by early postnatal adversity, and specifically that it negatively affects behavioral and biological development. Moreover, research suggests that the combined effects of prenatal and early postnatal adversity are worse than that of either alone. This is particularly germane to research on foster children because of the epidemiological evidence that the two may co-occur frequently among children in out-of-home care. Finally, a small but important evidence base suggests that just as a poor postnatal environment may exacerbate the effects of prenatal exposure, a good environment—one that may occur in the context of both conventional foster care and therapeutic foster care—has the potential to mitigate or offset prenatal exposure effects. However, because of the paucity of research in this area, more investigations are needed to replicate and extend the results obtained thus far.

RESILIENCE (I.E., TYPICAL DEVELOPMENT IN THE FACE OF ADVERSITY) IS EVIDENT IN ALL SAMPLES OF FOSTER CHILDREN (ALTHOUGH WHAT CONTRIBUTES TO IT IS NOT WELL UNDERSTOOD)

To this point in our discussion of research on foster care, we have focused largely on conclusions that can be drawn about the associations between early adversity and atypical development. However, it is equally important to consider two corollaries of this research: first, that some atypical

outcomes may be adaptive to the environmental circumstances of early adversity and foster care and second, that although atypical development is in general associated with adversity, it is far from ubiquitous; rather, typical development can and does occur even under conditions of significant adversity. That these issues are sometimes underemphasized or obscured in studies of foster children is not surprising. Although our culture does tend to celebrate the extraordinary instances in which individuals achieve great success amidst traumatic and neglectful childhoods, the prevalence and magnitude of problems observed among foster children may be more salient to researchers and other observers than the less frequent positive outcomes. Moreover, there may be concern that emphasizing positive outcomes could lead to less support from policy makers and the general public for programs that support this population.

Nevertheless, there is remarkably consistent empirical evidence that not all foster children fare poorly. Clearly, as we discuss later, some foster children manage to circumvent some or most of the expected negative outcomes. This line of investigation falls into the domain of resilience research, which has been a topic of considerable scientific interest in recent years (Rutter, 2006). The question of what might lead some individuals to emerge from early adversity relatively unscathed or even strengthened while others experience lasting effect has been a matter of considerable speculation (DuMont, Widom, & Czaja, 2007). Cultural models are often invoked with respect to the idea that some individuals' innate strength of character enables them to be successful even in the most difficult times (Masten, 2001). However, the science of resilience is considerably more developed and nuanced than that. In the scientific study of resilience in the general population, emphasis has been placed upon defining the individual/environmental variables most associated with positive outcomes, including personality characteristics (Flores, Cicchetti, & Rogosch, 2005), genetic polymorphisms (Rutter, 2003), strong caregiver relationships (Flores et al., 2005), and supportive parenting (Forgatch & DeGarmo, 1999).

There are several sources of evidence that resilient outcomes in the face of adversity are possible among foster children (Samuels & Pryce, 2008). Ironically, one source of evidence comes from the same sources of data that have been used to document the disparities of foster children. For example, in two earlier sections of this chapter, we highlighted the prevalence of poor psychological, developmental, and cognitive functioning and alterations in key domains of neurobiological development among foster children. However, these problems are by no means universal. One concrete example of the prevalence of resilient outcomes can be drawn from research on altered cortisol levels in foster children. This research has found that dysregulated diurnal cortisol-level patterns occur approximately three times as often in foster children than in the general population—a finding that may lead to the conclusion that this pattern is exhibited by most foster children. However, examination of the prevalence rates of foster children's diurnal HPA dysregulation reveals a different perspective: In two different samples, the low morning cortisol "blunted" pattern has been observed in only about 30% of the foster children (Bruce, Fisher, et al., 2009; Dozier et al., 2006). In other words, about 70% of foster children show typical patterns of diurnal cortisol production.

Moreover, although we tend to characterize low morning cortisol and blunted diurnal patterns as dysregulated, the fact that this pattern is associated with neglect in foster care and institutionalized samples (Carlson & Earls, 1997) suggests that it may be an adaptive response designed to conserve metabolic and other biological activity in the context of a nonresponsive rearing environment. Put another way, what we perceive from the perspective of typical development as dysregulated may be a strategy designed by nature to increase the likelihood of survival under adverse circumstances. In that sense, although we still may consider low morning cortisol to be atypical in the general population, it may be less appropriate to view it as pathological.

Corroborating evidence of resilience following early adversity can be found in the numerous studies of the catch-up that occurs among adopted children. Much of this work is focused not on foster care samples but on children who have experienced institutional rearing (Rutter, 1998). Notably, some of these children also experience foster care or multiple family placements before adoption, although the separate and additive effects of institutional and foster care have not been investigated.

In a remarkable meta-analysis that included a synopsis of more than 270 studies with a total of more than 230,000 adopted and nonadopted children and their parents, van IJzendoorn and Juffer (2006) found strong evidence for developmental catch-up in physical and emotional/psychological domains, especially for children adopted early. Although catch-up was often incomplete relative to nonadopted peers, the adopted children consistently fared far better than children who stayed in institutions. Interestingly, Croft, O'Connor, Keaveney, Groothues, and Rutter (2001) found that

catch-up in postinstitutionalized adoptees was associated with longitudinal improvements in the quality of the parent–child relationship.

The literature about specific predictors of resilience in foster children is surprisingly sparse. Healey and Fisher (2011) found that favorable outcomes, such as emotion regulation and academic adjustment in middle childhood, were more likely in foster children who during the preschool years had typical developmental status, particularly with respect to attention and executive functioning and who lacked environmental stress in early-childhood foster care.

Several studies have examined the nature of foster children's experiences while in care that may be associated with resilient outcomes. For example, a longitudinal investigation involving more than 3,000 children younger than age 12 years found factors that may improve placement stability, which is associated with positive outcomes, among foster children (Koh, Rolock, Cross, & Eblen-Manning, 2014). The factors contributing to foster care stability included the caregiver's dedication to the child's legal permanence, placement with a relative caregiver, and the absence of child mental health problems.

Kinship care also seems to be a protective factor for foster children (Farineau & McWey, 2011; Leathers, Spielfogel, Gleeson, & Nancy, 2012). For example, in a NSCAW subsample, long-term foster adolescents placed in kinship care were shown to have the lowest delinquency scores compared with other long-term foster adolescents (Farineau & McWey, 2011).

Kinship care may also help reduce the potential for the child to develop psychosocial problems. Landsverk et al. (1996) found psychosocial problems to be significantly higher for foster children in nonrelative (vs. kinship) placements, with foster children experiencing emotional and behavioral problems more frequently than kinship children (59.9% vs. 31.6%, respectively). This trend was also true for developmental and learning problems (24.2% vs. 15.8%, respectively). Finally, the foster children were also at higher risk for developing multiple types of problems and delays (28.0% vs. 14.5%, respectively).

Clearly, more research on the predictors of foster child resilience is needed. It is plausible that much of the research on resilience in the general population might apply to foster children as well. Given the availability of existing datasets in which to explore such issues by means of secondary analyses (e.g., NSCAW), this is an area in which progress may be readily achievable. In sum, it is clear that although foster and adoptive children may face increased risk for numerous negative outcomes, many display very high rates of resilience, especially when removed from circumstances of ongoing adversity and placed in stable, supportive, family-based care.

FAMILY-BASED CARE (INCLUDING FOSTER CARE) IS, AS A GENERAL RULE, BETTER THAN INSTITUTIONAL CARE

It is important to note that the foster care system is often maligned, in part because of the proliferation of research documenting atypical development and poor adjustment among foster children and to negative public perceptions about the foster care system. However, as was originally noted by Chapin (1926) and other early researchers and social activists, in spite of all its limitations, foster care allows children to be reared in a family setting. This appears to have significant advantages over institutional care and provides evidence of the central importance of family-based care to health development. Evidence about the advantages of foster care over institutional care can be derived from studies that have compared groups of children living in these different conditions by using the same measures of health and well-being. In this section, we review research on family-based care as an alternative to institutional care.

Child Care in Institutions

First-hand observations of institutional care for infants and young children describe conditions of profound deprivation. At a postwar United States institution, for example, infants ages 4 days to 24 months spent most of their time in cribs and rarely ventured outside the institution (Provence & Lipton, 1962). The younger group of infants ages 4 days to 8 months experienced the following:

> [They] shared the time and attention of the attendant with seven to nine other infants in the same age range for the eight-hour period of the day when she was present. For the remaining sixteen hours of the day there was no person in the nursery except at feeding time when an attendant who also had similar duties in other nurseries heated formulas, propped bottles, and changed diapers. Her presence could lead to no more than the briefest of contacts because she had twenty-five to thirty other babies for whom she must do the same before it was time to start over again. During an eight-hour day, five days a week . . . [the infant's] contact with [the attendant] was mainly in being taken from his crib to the work area once daily for bathing and dressing, and subsequently three or four times for a diaper change. (p. 27)

As is illustrated in this excerpt, the caregivers interacted with the children to fulfill only the most basic instrumental needs, such as feeding, diapering, and bathing. These interactions offered few opportunities for social engagement: Infants younger than age 8 months were fed by a "propped bottle" rested against padding in their crib, and older infants were spoon-fed for 6–8 minutes each while caregivers talked amongst themselves (Provence & Lipton, 1962). The caregiving staff "seemed to like the babies" and "gave as much of themselves as they could" in overworked conditions (p. 29), but shifting staff schedules and turnover meant that many infants were not regularly assigned to the same caregivers. Strict routines for feeding, diapering, and bathing, along with a paucity of adult supervision, meant that each infant "had very few experiences in having the adult respond to his needs (e.g., the discomfort of hunger) at the time he expresses them." (p. 19). Perhaps not surprisingly, Provence and Lipton noted "an almost startling quietness" in the nursery (p. 89), an indication that the infants learned to not seek adult attention under either playful or distressed conditions.

Based on this brief depiction, it is clear why Nelson, Fox, and Zeanah (2014) argued that institutionalization "represents a form of neglect, albeit a very extreme form" (p. 306) and that children in contemporary institutional care "lack supervision and structure, necessary social interaction and emotion regulation, cognitive and language stimulation, access to adequate nutrition, and so on" (p. 306–307). Echoing the postwar findings of Provence and Lipton (1962), observations of a Romanian institution in the 1990s found that children had limited opportunities to interact socially with caregivers (Nelson et al., 2014). They had long stretches of unstructured playtime, in which the caregivers mostly chatted amongst themselves, ignoring the large number of children wandering aimlessly. Over the course of a day, a child would likely have contact with multiple adults, which precluded consistency or the opportunity for sustained interaction. In a given week, a child could have come in contact with 17 different caregivers, three housekeepers, four nurses, two educators, one physician, one psychologist, and one physical therapist (Nelson et al., 2014; pp. 34–35). Although the conditions of institutional care vary widely within and across countries, the institutions studied by Nelson et al. in Bucharest shared a routinized daily schedule, a high child:caregiver ratio, and staff with little formal training in child development.

By contrast, foster caregiving typically involves one or two primary caregivers—extended family members, if possible—who have, under ideal circumstances, made an investment to provide personalized care for the child. Natural variability in caregiving quality across foster caregivers notwithstanding, children living in foster care can reasonably expect that their primary caregivers will respond to their basic needs. A major question is the extent to which typical development can occur in the absence of a relationship with a primary caregiver.

A Comparison of Foster and Institutional Care: The Bucharest Early Intervention Project

Although research in the twentieth century has demonstrated that children raised in institutions show impairments across a variety of developmental domains, the inferences that can be drawn from these studies are necessarily limited by a lack of an experimental control (Zeanah et al., 2003). Without random assignment, it remains possible that infants who are abandoned to institutions began life with more severe disadvantages than noninstitutionalized children or that the more-advantaged infants get adopted from institutions, leaving behind their most disadvantaged peers. As a result, sample bias (vs. institutionalization itself) could explain the detrimental outcomes found among this population.

In 2000, a landmark, randomized controlled longitudinal study was launched that investigated foster care as an alternative to institutional care: the Bucharest Early Intervention Project (BEIP; Nelson et al., 2014). The BEIP is remarkable because the circumstances in Romania at the time when the study began allowed the researchers to randomly assign children to ongoing institutional care (n = 67) or to family-based foster care (n = 69; Zeanah et al., 2003). Although the foster families received some training (Smyke, Zeanah, Fox, & Nelson, 2009), the conditions did not allow for foster care to be enhanced in terms of ongoing support and treatment for the children. Thus, this study represents a scientifically rigorous comparison of institutional versus family-based rearing development. The BEIP results provide remarkably consistent evidence that institutionally raised children fare worse than foster children across numerous domains in which foster children show atypical development, including emotional, psychological, physical, and neurobiological development.

The BEIP assessed children at baseline (before age 31 months) and at ages 30 months, 42 months, 54 months, and 8 years. Some children were as young as age 6 months when the intervention began. At the first assessment, some of the children had as many as 24 months of the intervention, while the older children had a few months or less. In addition to the two randomly assigned groups, a third group of

72 noninstitutionalized, matched community comparison children who lived with their biological parents was also assessed at each study wave. This permitted researchers to evaluate developmental catch-up among the foster children (Zeanah et al., 2003).

Over the course of the study, some of the institutionalized children were adopted or entered foster care. Analyses were conducted on an *intent-to-treat* basis, such that (for example) a proportion of children in the institutionalized group at age 8 years were living in family-based care (Nelson et al., 2014). Thus, the findings that are reviewed in the next sections represent conservative estimates of the effects of institutionalization on child outcomes.

Cognition and Language

The children who remained in institutional care until age 8 years demonstrated significant declines and delays in all domains of cognition, including intellectual function, executive function, memory, and language (Nelson et al., 2014). On measures of intellectual function, the children placed in foster care demonstrated higher mean IQ scores on the Bayley Scales (at 42 months) and on the Wechsler Preschool and Primary Scale of Intelligence (at 54 months) than did their institutionalized peers (Nelson et al., 2007). The lesser time the children spend on institutional care, the better their IQ performance. Specifically, children needed to have been assigned to foster care before age 24 months to outperform their institutionalized peers on the intelligence measures. The intervention effects on IQ were not as strong at age 8 months as at ages 42 and 52 months, an indication (perhaps) of the modest gains in IQ among institutionalized children who were placed in newly designated government foster homes between the 54-month and 8-year assessments (Fox, Almas, Degnan, Nelson, & Zeanah, 2011).

In some cognitive domains, foster children's capacities were superior to institutionalized children's but below those of their community peers. Despite their advantages in IQ over institutionalized children, foster children's IQ scores were lower than the community control children's on all Wechsler Intelligence Scale for Children subscales at age 8 years (Fox et al., 2011). Similarly, on assessment of inhibitory control at age 54 months, the foster children scored higher than the institutionalized children did but lower than the community comparison group did (Nelson et al., 2014).

In the case of other executive-function skills measured with the Cambridge Automated Neuropsychological Test and Battery at age 8 years, the institutionalized children performed worse than the community comparison children on visual memory and executive functioning tasks (Bos, Fox, Zeanah, & Nelson, 2009). The foster children and institutionalized children assigned to ongoing institutional care performed equivalently on all memory and executive-functioning domains except spatial working memory. After controlling for birth weight, head circumference, and duration of time spent in the institution during infancy, spatial working memory performance favored the foster group.

In the BEIP, language assessments across time indicated that the foster care intervention remediated the severe language deficits associated with ongoing institutional care, if placement occurred early enough. Compared with the institutionalized children, the foster children demonstrated better expressive and receptive language skills at ages 30 and 42 months (Windsor et al., 2011). The language-development benefits continued for foster children through the 8-year assessment (Windsor, Moraru, Nelson, Fox, & Zeanah, 2013).

Socioemotional Development

Given the profound absence of emotionally salient, consistent, and contingent social interaction with caregivers in the institutions, the BEIP investigators anticipated that the institutionalized children would show detriments in attachment to caregivers and in the experience and expression of emotion in social contexts. Indeed, foster children (vs. institutionalized children) expressed more joy during Laboratory Temperament Assessment Battery (Goldsmith & Rothbart, 1999) tasks at ages 30 and 42 months and exhibited more improvements in positive emotion during this period (Ghera et al., 2009). Notably, foster children showed even more positive emotion and attention to tasks at age 42 months (Ghera et al., 2009). Institutionalized children demonstrated low levels of attention to the positive emotion-eliciting tasks at ages 30 and 42 months (Ghera et al., 2009). The lower levels of attention and positive emotion expression among the institutionalized children care may relate to disruptions in the neural circuitry involved in emotion processing (Parker & Nelson, 2005). By contrast, the recovery observed among foster children provides evidence for the relative plasticity of neural circuits that support positive affect (Ghera et al., 2009).

The disruption of attachment in institutionalized children was severe. At the baseline assessment, investigators assessed attachment behaviors in the community comparison sample and a subset of 95 institutionalized children ages 12–31 months who had spent an average of 90% of their lives in institutional care (Zeanah,

Smyke, Koga, Carlson, & Bucharest Early Intervention Project Core Group, 2005). The Strange Situation Procedure (Ainsworth, Blehar, Waters, & Wall, 1978) was administered with these institutionalized infants and their preferred caregiver (if none could be identified, it was the caregiver who worked with the child most regularly). In addition to deriving a categorical attachment classification from the Strange Situation Procedure, a continuous, 5-point rating of attachment behavior was assigned by two experts (Zeanah et al., 2005). Compared with the community children, who were classified as 74% secure and 22% disorganized, the institutionalized children were classified as 18% secure, 65% disorganized, and 12.6% *unclassified*, a rare designation meaning that there were too few attachment behaviors to assign a child to any group (Zeanah et al., 2005). Using the continuous rating scale, investigators confirmed that 65% of institutionalized children exhibited "anomalous behaviors only minimally related to attachment" (Nelson et al., 2014, p. 244). In addition, 9.5% of the institutionalized children "had no discernible attachment behaviors whatsoever" (Nelson et al., 2014, p. 244).

At 42 months of age, BEIP intervention effects on attachment and social behaviors among foster children were substantial. Secure attachment at age 42 months was exhibited by 18% of institutionalized children, 65% of community children, and 49% of foster children (Nelson et al., 2014). Foster children also showed significantly fewer signs of an emotionally withdrawn and inhibited type of reactive attachment disorder than did institutionalized children; levels of this subtype were comparable between foster and community children after age 30 months (Smyke et al., 2012). Regarding timing effects, secure attachment at age 42 months was more prevalent among children assigned to foster care at or before age 24 months than among those placed later (Smyke, Zeanah, Fox, Nelson, & Guthrie, 2010). Similarly, children assigned to foster care at or before age 20 months were rated by teachers as significantly more socially skilled with peers at age 8 years than were those placed later (Almas et al., 2012).

Psychopathology

The impact of severe psychosocial deprivation on the development of psychopathology in institutionalized children was predictably detrimental. At age 54 months, 53.2% and 27.0% of institutionalized children were diagnosed with psychiatric and behavioral disorders, respectively, compared with 22.0% and 6.8% of community children (Nelson et al., 2014). In the case of ADHD, institutionalized children in the BEIP study demonstrated more symptoms of inattention and impulsivity at age 8 years than did community children (McLaughlin et al., 2014). This effect of early psychosocial deprivation on ADHD symptoms was mediated by reductions in cortical thickness in several regions of the prefrontal, parietal, and temporal cortices (McLaughlin et al., 2014).

Foster care tended to improve mental health outcomes when compared with institutional care, but with several qualifications. First, at age 54 months, foster children had fewer internalizing, but not externalizing, disorders than did institutionalized children (Zeanah et al., 2009). Second, this was true only for foster girls (Zeanah et al., 2009). The effect of foster care on internalizing disorders in girls was mediated by secure attachment at age 42 months (Nelson et al., 2014). Nelson et al. identified a number of other psychobiological moderators of BEIP intervention effects. A particularly important finding to note is that the timing of assignment to foster care did not moderate the effect of intervention on psychopathology. Even children who entered foster care relatively late were protected from the effects of early deprivation on anxiety and depression (Zeanah et al., 2009).

The Caregiving Conditions Necessary for Typical Development

Findings from the BEIP and related longitudinal research on internationally adopted children (Rutter, Kumsta, Schlotz, & Sonuga-Barke, 2012) point to specific developmental domains that have more or less plasticity in response to early deprivation. These studies provide many insights: We highlight only a few here, along with their implications for intervention with children exposed to early adversity.

First, it appears that children can form attachments with primary caregivers even after accumulated early experiences with institutional caregivers who, because of their context, were by definition not able to provide sufficiently responsive or emotionally salient interaction. Clearly, this is an area in which earlier intervention is better. In the BEIP, catch-up in attachment security was significantly more common among foster children placed before age 24 months than among children placed later. A meta-analysis of research on adopted children found an even more stringent age cut-off of 12 months, by which children must be adopted to catch up to the attachment security of their nonadopted peers (van IJzendoorn & Juffer, 2006). In turn, secure attachment was associated with a range of short- and long-term psychosocial benefits for foster and adopted children. These findings suggest that the earlier a

child with unstable living arrangements can be placed with a primary caregiver, the better.

Second, in terms of other domains of development, the timing of placement into foster care was important for some but not for others. For instance, attachment security, IQ, language skills, electroencephalogram measures, stereotypies, and other domains were sensitive to the timing at which children began to live in family-based care, with earlier placement generally being more beneficial (Bos, Zeanah, Smyke, Fox, & Nelson, 2010; Zeanah, Gunnar, McCall, Kreppner, & Fox, 2011). Interestingly, family-based care was protective of anxiety and depression no matter what age children were assigned to foster care (Zeanah et al., 2009), though this finding must be interpreted with caution: No child was older than age 3 years when placed into family-based care. It is possible that adoption at a later age may not be protective in terms of internalizing disorders. Nevertheless, this finding highlights the influence of the family caregiving environment on difficulties that are often attributed to inherited biological predispositions.

Third, family-based care was beneficial for BEIP children's cognitive development (Nelson et al., 2007) but did not protect them from difficulties with executive functioning, inattention, and hyperactivity (Bos et al., 2009; McLaughlin et al., 2014). In their longitudinal study of adopted children, the ERA team also found that inattention/hyperactivity was part of a constellation of difficulties, persistent into adolescence, labeled as *deprivation-specific psychological patterns* (Kreppner et al., 2010; Kumsta et al., 2010). Institutionalized children may have experienced more adverse prenatal experiences that detrimentally influenced neurodevelopment prior to children's entrance into the orphanages. Regardless, these findings suggest important targets for intervention.

To mitigate the executive function deficits associated with early deprivation, ordinary caregiving provided by foster and adoptive families may have to be enhanced or supplemented with specific interventions designed to improve the functioning of children's neural systems and attendant behaviors (Fisher & Gunnar, 2010; Gunnar, 2010). Nevertheless, the results of the BEIP are critically important because they indicate that typical development seems to require, as a basic condition, the presence of a primary caregiver. Although the most optimal arrangement may be a permanent biological or adoptive parent, it is not always possible to quickly resolve issues of permanency. Within this context, the evidence base is strong that foster care appears to enhance current and future health and well-being more than does institutional care.

FAMILY-BASED INTERVENTIONS THAT CAN MITIGATE THE EFFECTS OF EARLY ADVERSITY

If a general conclusion of foster care research is that temporary placement in family-based care falls somewhere in the continuum between conditions that promote optimal development care and institutional care, then a related question is how to shift the location on the continuum represented by foster care in a positive direction through interventions. This is a key question from a public policy standpoint and from a scientific perspective inasmuch as it relates to questions about the malleability or plasticity of the biobehavioral systems negatively affected by early adversity. There is a fairly extensive literature in this area, although much of this work has not used randomized experimental designs. A recent systematic review using the Cochrane Collaboration's criteria (Turner & Macdonald, 2011) noted that only five studies met the criteria for an evidence-based program for foster families. Further, a study by the Office of Victims of Crimes suggested that only 1 of 24 mental health interventions for children who had been abused is effective (Saunders, Berliner, & Hanson, 2004).

Foster care families have unique needs that determine which interventions are likely to remediate the effects of early adversity on healthy development. First, because foster children have been exposed to neglectful or abusive parenting prior to their entry into care, in any foster care intervention the caregiver receiving the intervention services does not have a shared history with the child. Further, the foster caregiver may already have a set of parenting skills that are generally effective. Second, because of their maltreatment histories, foster children are more likely to exhibit constellations of behavioral, neurobiological, and relationship vulnerabilities that pose unique challenges to caregivers. Thus, standard parenting intervention programs might not be sufficient or appropriate for improving child outcomes. Third, children enter foster care at varying ages and have likely experienced multiple prior caregiving situations. This may lead foster children to enter care with their own set of expectations and demands based on their histories.

Leve et al. (2012) conducted a systematic review of intervention programs that have been tested with foster families and shown to improve child outcomes. The interventions included in the review met the following criteria: evaluated using a randomized, controlled trial; produced at least one positive outcome; randomized at the level of the individual; and included at least 15 children per group. Eight interventions met these criteria. We describe seven of those interventions (the eighth—BEIP—was described

in an earlier section of this chapter), along with two others (meeting these criteria) that were published after the Leve et al. review. Five of these interventions emanated from the same research group at the Oregon Social Learning Center (OSLC) and are reviewed together, followed in developmental order by four evidence-based programs from other research groups. (Please note that the lead author of this chapter is one of the developers of several of the OSLC interventions.)

Treatment Foster Care Oregon for Adolescents (TFCO-A)

TFCO-A, the first intervention developed by the Oregon group, consists of a multicomponent program that involves individual placement with a specialized foster family for adolescents being removed from their homes (Chamberlain, 2003). Typically, TFCO-A adolescents have maltreatment histories and serious, chronic problems with delinquency. In TFCO-A, adolescents are placed in community homes where the foster caregivers are intensively trained, supervised, and supported to provide positive adult support and mentoring, close supervision, and consistent limit setting. TFCO-A placements typically last 6–9 months and involve coordinated interventions at home, with peers, in educational settings, and with the adolescent's long-term placement resource. The results from TFCO-A trials in the United States indicate its effectiveness in reducing arrest rates and deviant peer affiliations for boys and girls; placement disruptions and parenting for boys; and pregnancy rates, depressive symptoms, psychotic symptoms, and school engagement for girls (Chamberlain & Reid, 1998; Harold et al., 2013; Kerr, Leve, & Chamberlain, 2009; Leve, Fisher, & Chamberlain, 2009; Poulton et al., 2014). For example, between baseline and a 12-month follow-up, the TFCO-A adolescents had spent 53 (boys) and 22 (girls) days in lockup (e.g., a detention facility) versus 129 and 56 days, respectively, for the control adolescents. In addition, long-term effects have been found on drug use at 7 years postintervention (Rhoades, Leve, Harold, Kim, & Chamberlain, 2014). Several international replications of TFCO-A have shown positive results. For example, a trial in Sweden indicated significant reductions in youth-reported externalizing and internalizing behavior (Westermark, Hansson, & Olsson, 2010).

Multidimensional Treatment Foster Care for Preschoolers (TFCO-P)

TFCO-P is a downward extension of TFCO-A for preschool-age foster children. It uses a behavior-management approach and trains, supervises, and supports foster caregivers to provide positive adult support and consistent limit setting. This support and training occurs through weekly parenting groups, individual therapy, family therapy, and 24/7 on-call support and typically lasts 6–9 months. Similar to TFCO-A, it also coordinates with the child's biological parents, with the assumption that the end goal is reunification. The randomized trial of TFCO-P showed that the intervention improved child attachment behavior: TFCO-P children demonstrated increased secure behavior and decreased avoidant behavior relative to children in regular foster care (Fisher & Kim, 2007). TFCO-P also improved stress–response systems, preventing blunted diurnal cortisol patterns among the intervention children (Fisher et al., 2007) and reducing caregiver stress (Fisher & Stoolmiller, 2008). Further, TFCO-P improved placement stability outcomes across a 2-year period and mitigated the risk of influence of multiple prior foster placements on subsequent placement failures (Fisher et al., 2005). Compared with the TFCO-P children, the control children (in regular foster care) were 3.6 times more likely to experience a permanent placement failure.

Kids in Transition to School (KITS)

KITS evolved from the TFCO-P intervention as a short-term, readily scalable intervention focused on school readiness and improved school functioning for foster children (Pears, Fisher, & Bronz, 2007; Pears, Fisher, Heywood, & Bronz, 2007). The KITS intervention occurs in two phases: a school readiness phase (2 months before kindergarten entry) focused on preparing children and caregivers for school and a transition/maintenance phase (first 2 months of kindergarten) focused on supporting a positive transition to school. The intervention includes a group-based program for the children (24 sessions) focused on promoting early literacy and socioemotional skills and a parent-based program (8 sessions) focused on promoting caregiver involvement in early literacy and school. Compared with regular foster care services, KITS has been shown to increase foster children's early literacy and self-regulatory skills (Pears et al., 2013) and to reduce child oppositional and aggressive behavior in the classroom (Pears, Kim, & Fisher, 2012).

Keeping Foster Parents Trained and Supported (KEEP-SAFE)

KEEP-SAFE shares the foster–caregiver component of the TFCO programs described earlier but, like KITS,

was designed to be a less intensive intervention for foster families with school-age children. In the randomized trial of KEEP-SAFE, foster caregivers receiving a new placement were randomly assigned to regular foster care services or to the KEEP-SAFE parenting intervention (Chamberlain et al., 2008). The KEEP-SAFE intervention lasts 16 weeks and includes foster caregiver meetings with 8–10 foster caregivers that are focused on training, supervision, and support for applying behavior management strategies. KEEP-SAFE has been shown to effectively reduce child problem behavior. These child behavior problem reductions were associated with intervention-driven improvements in parenting (Chamberlain, Price, Reid, & Landsverk, 2008). Similar to TFCO-P, KEEP-SAFE also improved placement stability: KEEP-SAFE mitigated the risk-enhancing effects of prior multiple placements (Price et al., 2008), and the KEEP-SAFE children were more likely to be reunified with their biologic parents or permanently placed with relatives or an adoptive family (17% of the KEEP-SAFE children vs. 9% of the control children).

Middle School Success (MSS)

The final intervention originating from the OSLC team is MSS, a derivative of KEEP-SAFE that targets youths exiting primary school (Chamberlain, Leve, & Smith, 2006). MSS includes foster–caregiver and youth components in the summer prior to middle-school entry (six sessions) and through the first year of middle school (weekly). The parenting sessions were group based and behavior-management oriented; the youth sessions were group based (summer) and individually based (school year) and were oriented toward skill building. Relative to the children in regular foster care, the MSS children exhibited decreased externalizing and internalizing problems at the 6-, 12-, and 24-month follow-ups (Kim & Leve, 2011; Smith, Leve, & Chamberlain, 2011). MSS also resulted in increased prosocial behavior and fewer placement changes at the 12-month follow-up, reduced substance use and health-risking sexual behavior at the 36-month follow-up (Kim & Leve, 2011), and improved decision making at the 5-year follow-up (Weller, Leve, Kim, Bhimji, & Fisher, 2015).

Attachment and Biobehavioral Catch-Up (ABC)

ABC is one of three interventions shown to be effective during early childhood (BEIP and TFCO-P being the other two). It is a 10-session intervention designed to help caregivers facilitate healthy regulation of foster child behavior and stress responses by teaching foster caregivers to be highly responsive to child emotions and to increase their provision of nurturing care and promotion of attachment security during early childhood (Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008). The results of a randomized trial of ABC indicated that the intervention children were more often secure and less often disorganized in their attachments to caregivers than were the control children: 52% (vs. 33%) exhibited secure attachment and 32% (vs. 57%) exhibited disorganized attachment approximately 1 month after the intervention (Bernard et al., 2012). ABC has also shown success in normalizing foster child stress responses (i.e., cortisol reactivity) relative to the control children, which indicates the plasticity of their neurobiological systems and the capacity for recovery. Overall, the ABC findings parallel the TFCO-P effects on attachment and stress responsivity but extend downward developmentally to the infant and toddler period.

The Incredible Years

The Incredible Years is an effective intervention for at-risk children and children with conduct problems that was modified for foster families with school-age children (Reid, Webster-Stratton, & Hammond, 2003; Webster-Stratton, Reid, & Hammond, 2001). The modified Incredible Years intervention incorporates a coparenting component between foster and biological caregivers to expand their knowledge of each other and their child, practice open communication, and negotiate interparental conflict regarding topics such as family visitation, family routines, and discipline (Linares, Montalto, Li, & Oza, 2006). The results suggest that Incredible Years improves foster caregivers' positive discipline and coparenting skills.

Fostering Individualized Assistance Program (FIAP)

The FIAP is focused on wrapping services around the child according to their individual and family needs, with the goal of improving placement stability and reducing behavioral and emotional problems (Clark et al., 1994). The FIAP has four components, including a strengths-based assessment, life-domain planning, clinical case management, and follow-along supports and services. The FIAP children were shown to exhibit fewer attention, withdrawal, and total problems at an 18-month follow-up (assessed via caregiver report; Clark et al., 1994). In addition, the FIAP children had fewer runaways and spent less time incarcerated. Increased placement stability has been found for older FIAP children only (Clark et al., 1998).

Fostering Healthy Futures (FHF)

FHF was designed for maltreated foster children ages 9–11 years (Taussig, Culhane, & Hettleman, 2007). The program promotes child well-being by identifying and addressing mental health issues, preventing adolescent risk behaviors, and promoting competence. The intervention consists of 90-minute therapeutic skills groups for the children over 30 weeks during the school year, combined with one-on-one mentoring (2–4 hours/week) with a graduate student. FHF has been shown to reduce child mental health problems and reduce symptoms of dissociation 6 months postintervention (Taussig & Culhane, 2010). In addition, the FHF children reported better quality of life immediately following the intervention, and fewer FHF youths had received recent mental health therapy 6 months postintervention (Taussig & Culhane, 2010). Finally, the FHF youths were 71% less likely to be placed in residential treatment 1 year postintervention (Taussig, Culhane, Garrido, & Knudtson, 2012).

Limitations of Existing Foster Care Interventions

Although the nine interventions reviewed in the preceding sections offer promise for improving outcomes for foster children, there are limitations in the work to date. First, there is a lack of long-term follow-up data: five studies do not have published follow-up data beyond a 12-month follow-up period (ABC, Incredible Years, KEEP, KITS, and FPF), and only three have published effects beyond 24 months (TFCO-A, BEIP, and MSS), making it difficult to know whether the observed effects sustain across development. In at least one of these interventions (Incredible Years), the effects dissipated quickly: 3 months after the intervention ended, only the positive discipline effect remained. Further, the length of time between intervention completion and the outcome assessment was often unclear from the published work. For example, the ABC samples had a wide child age range; therefore, the outcome assessment was delayed if the child was younger at the start of the study. In addition, some children in all of the studies experienced one or more placement changes prior to the outcome assessment. Together, these limitations cast doubt about whether the foster children who benefited from intervention will exhibit healthy adjustment later in development. Long-term follow-up studies are needed to better evaluate whether initial effects of such interventions are maintained over time.

Second, the effects found across studies did not consistently generalize to other measures. For example, the FIAP effects on child mental health were present for caregiver reports but not for youth reports, and delinquency outcomes in TFCO-A were present for girls using days-in-locked-settings data but not using self-reported delinquency data. The effects were also sometimes specific to subpopulations (e.g., one gender, older children; FIAP and TFCO-A) or to one set of hypothesized outcome constructs but not to another set (MSS and FIAP). Given these inconsistent findings and the generally small effect sizes (and the failure to report effect sizes in many published reports), there is room for refinement. Efforts to identify patterns of behavior among nonresponders might yield useful insights into how effective interventions could be modified or adapted to further remediate the negative effects of early adversity.

Summary

In summary, at least nine interventions for foster families have been tested using randomized trial designs at the individual level and have been shown to be effective in improving one or more outcomes for foster children. The results from most of these studies have shown small to moderate effect sizes that decrease over time. TFCO-A is an exception to this pattern, as is BEIP, reviewed in an earlier section of this review.

Although these interventions vary in content and target age, they converged around several domains, including being developmentally specific, aiming to reduce known risk factors and promote resilience, and emphasizing the mediating role of parenting in linking early adversity with child outcomes. Of note, the positive effects of the interventions varied based on the developmental period of the children receiving the services. For example, two of the interventions reviewed here (TFCO-P, ABC) and BEIP reviewed in an earlier section showed positive effects on parent–child attachment relations and child neurobiological development in early childhood. Conversely, nearly all the middle-childhood and adolescent interventions showed positive effects on behavior problems (TFCO-A, KEEP, MSS, and FIAP), but only MSS had documented effects on an aspect of neurobiological functioning (decision making; Weller et al., 2015). Whether this is a function of the respective assessment measures in each study or a function of reduced neural plasticity across development is a question for future research. Taken together, however, the results of the interventions reviewed here provide strong evidence that the domains of functioning affected by early adversity in foster children appear to remain, at least to some degree, pliable throughout development.

CONCLUSIONS, TRANSLATIONAL IMPLICATIONS, AND DIRECTIONS FOR FUTURE RESEARCH

In any comprehensive, complex review of the literature, it can be challenging to synopsize points into a manageable set of conclusions. However, if such an effort is to prove useful—not only for summarizing the current state of a scientific knowledge base but also for pointing to directions for future research—a parsimonious perspective on the field is necessary. Several main inferences on typical and atypical development can be made from the foster care literature:

First, foster care research adds to the general understanding about the effects of early adversity on development and to specific studies documenting that early adversity effects (beginning prenatally) are cumulative, with those occurring earlier and for longer periods having the greatest impact. This research replicates and extends the findings in other areas (including research on animals and humans) with respect to the pervasive impact of early adversity on typical development. In particular, it highlights that development can get off course from not only traumatic events that occur in the life of the child, but also the absence of expected environmental input in the form of nurturing and responsive care (i.e., neglect). One disclaimer is that when considering the tendency for there to be poorer outcomes for foster children, it is important to bear in mind that foster care is typically an outcome of adversity rather than the cause of poor adjustment, although certain experiences in foster care can exacerbate the impact of early adversity.

Foster care research further makes clear that the disruptions to typical development emanating from early adversity may affect broad and interrelated domains of psychological and biological functioning. Of particular note is the finding that early neglect appears to disrupt the development of neuroendocrine systems that play a critical role in maintaining homeostatic balance in the presence of stress. This may help explain the vulnerability to future stress that has been observed among individuals exposed to early adversity. In addition to neuroendocrine effects, early adversity appears to affect the structure, function, and possibly the connectivity among crucial brain regions that underlie key capacities such as executive functions and threat detection.

One of the unique aspects of foster care research with respect to elucidating the effects of early adversity on child development is that it enables us to understand the effects of specific dimensions of adversity on particular underlying neurobiological systems. The aforementioned results related to the effects of placement transitions on executive functioning are one example of this. One important future direction for foster care research is to continue to explore the impact of specific types of early adversity that occur more commonly in foster care. For example, children who experience prenatal ethanol exposure and subsequently spend their early years in a succession of foster homes with different caregivers might be examined in comparison with those remaining with their biological parents and those adopted at birth. This would allow for a much more precise understanding of the combined effects of prenatal teratogenic exposure and early adversity than currently exists. It will be especially important for work in this area to be multilevel in nature, thereby continuing to contribute to the translational knowledge base that exists with respect to the psychological and biological effects of adversity.

Second, foster care research provides conclusive evidence that, despite the health risks posed by early adversity, typical development can occur under less than optimal rearing conditions. On average, foster children fare poorly on many measures of well-being. However, as is nearly ubiquitous in studies of foster children, some individuals' development appears relatively on course despite significant early adversity. From an evolutionary perspective, our ability to survive as a species would certainly have been reduced were this not the case, but it can still be easy to overlook this phenomenon given the extent to which the risks associated with being in foster care (or other forms of adversity) are highlighted in the literature and media. Historically, such positive outcomes have been vaguely attributed to defined concepts of innate resilience. Research in this area poses methodological challenges; however, it is important that future investigations focus on better understanding the variables, especially those that are malleable, that increase the likelihood of typical development following early adversity. Such variables may exist at many levels. Thus, research will do well to focus on the constitutional and environmental influences on resilience and on the complex interrelations among these influences.

Third, foster care research suggests that, when early adversity leads development off course, subsequent improvements in environmental conditions have the potential to realign trajectories positively. Further, although early intervention seems to produce positive change, environmental improvements later in development can have a positive impact.

These intervention studies do more than inform foster care policy. Studies of this nature provide proof of concept

about the plasticity of behavior and biology—even in the context of deterministic life circumstances. Several disclaimers are necessary, however, in this area. First, not all children whose development is compromised by early adversity respond to interventions. In particular, it appears that as adverse experiences accumulate—especially in the context of combined prenatal and early adversity—they may limit the plasticity of these systems. In addition, genetic factors are likely to play a role. Because most research on interventions has been focused on detecting main effects, the knowledge base in this area is limited and more work is needed to better understand the variables associated with recovery from the effects of early adversity. Second, it is important to point out that the foster care intervention research on biological plasticity following adversity is quite limited and focuses primarily on the HPA axis. Moreover, at this point, the biological evidence comes only from studies of infants and young foster children. It is not clear at present whether the same plasticity can be observed in other biological systems or in older foster children.

Several additional issues warrant attention with respect to what foster care intervention research can tell us about typical and atypical development. First, although the ability to mitigate the effects of early adversity is evident in this research, the specific intervention mechanisms at work are far less well understood. The existing evidence-based interventions for foster children typically consist of multiple components that focus on the child and caregiver. Although the interventions are theory based, the existing studies provide only limited information about whether the interventions effectively target the domains hypothesized to be most necessary to affect outcomes. With numerous intervention components, it may be that some produce more of an impact than others do. However, because studies evaluating these interventions are quite costly and take many years to conduct, the ability to deconstruct interventions and test the impact of their individual and combined components is limited.

A related issue is to examine for whom interventions are most effective. There is no question that the development of a scientific knowledge base within the foster care literature showing that the effects of early adversity can be mitigated is a major accomplishment. Yet we know that these interventions are not universally effective and that it may be possible to identify certain phenotypes that are more or less likely to respond to existing interventions. Work in this area is fundamentally translational in nature because it reciprocally informs our understanding of how to best support foster children and our understanding of issues related to individual differences in neural and behavioral plasticity.

In this chapter, we have attempted to characterize the foster care research literature as it pertains to typical and atypical development. Although many of the conclusions should create ongoing concern and motivate continued efforts to reduce adversity in all children, there is also reason for optimism, both in terms of the clear ability of some children to overcome adversity and in terms of the extant knowledge base about how to facilitate positive outcomes. The ongoing research in this area will likely continue to inform this topic; as such, future updates of this discussion are warranted.

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CHAPTER 13

Memory Development, Emotion Regulation, and Trauma-Related Psychopathology

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For in the end, it is all about memory, its sources and its magnitude . . .

— Elie Wiesel, *Night*

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Our chapter concerns developmental psychopathology and autobiographical memory development. We especially focus on links among child maltreatment, trauma-related psychopathology, and memory. Our main tenet is that memory development can be influenced by childhood trauma (child maltreatment being the main type of trauma we discuss) and by the emotion regulation problems and trauma-related psychopathology that may result from that trauma. More specifically, we contend that children and adults with child maltreatment histories, like individuals without such histories, often have particularly accurate memories for trauma-related life events. In fact, histories of trauma may heighten memory for trauma-related information. However, individual differences also exist, leading at times to autobiographical memory deficits in a subset of individuals who experienced childhood maltreatment. Of importance, these deficits do not appear to be directly related to child maltreatment per se but instead are predicted by certain emotion regulation strategies that are associated with trauma-related psychopathology.

This chapter provides a selective review of research relevant to our thesis. We begin by presenting a conceptual framework for considering empirical findings. Based

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on a developmental psychopathology perspective, we then ground the reader in theories and research on typical development of memory and emotion regulation processes. Effects of child maltreatment, particularly in relation to trauma-related psychopathology in children and adults, are then described, with a special focus on post-traumatic stress disorder (PTSD), dissociation, and depression. This is followed by a brief discussion of the psychophysiology and neurobiology of trauma as related to autobiographical memory development. Then, we describe theories that provide potential reasons why child abuse victims may have particularly accurate memories of trauma-related information, followed by a review of theories pertaining to why a subset of child maltreatment victims show impaired memory. Next, we present our autobiographical memory development model that places emotion regulation at the forefront of understanding individual differences in autobiographical memory in relation to psychopathology. Afterward, we review research findings with regard to child maltreatment and memory development. We conclude with comments on the translation of this research into practice and on future research needs. Although some ideas we mention in this chapter include elements of speculation, we hope that this review will stimulate future theory and research.

CONCEPTUAL FRAMEWORK

Goodman, Quas, and Ogle (2010) proposed a conceptual framework for thinking about maltreatment and memory, a framework that we expand and then rely upon in the present paper. The framework is largely heuristic, but it helps us in organizing and interpreting relevant theory and empirical research. Our original conceptualization included two dimensions along which studies vary. The first dimension concerns the type of stimulus or to-be-remembered information, and the second concerns the life experiences and background of the participant in question. For simplicity, these dimensions can be represented by a 2 (type of stimulus) × 2 (childhood background) factorial classification scheme. However, given growing evidence regarding the important roles of emotion regulation and related psychopathology in memory, we expand on the conceptualization here to better incorporate emotion regulation/psychopathology. Specifically, we propose a 2 (type of stimulus) × 3 (childhood background/emotion regulation strategy) factorial classification scheme.

Considering first the type-of-stimulus dimension, in many studies, the to-be-remembered stimulus is fairly neutral or even mildly positive (e.g., stories, brief interactions with an adult; Goodman, 1980; Quas et al., 2007). But in other studies, the to-be-remembered information is distressing or trauma related (e.g., stressful medical procedures, anogenital examinations, trauma narratives; Lanious et al., 2006; McWilliams, Goodman, Lyons, Newton, & Avila-Mora, 2014; Merritt, Ornstein, & Spicker, 1994; Saywitz, Goodman, Nicholas, & Moan, 1991). This difference in stimulus type can have a profound effect on memory (Christianson, 1992), regardless of the childhood history of the person under study.

The second dimension that we originally proposed concerns participants' backgrounds: that is, whether or not they experienced childhood trauma or have a history of maltreatment. In most memory studies, the participants do not have any known histories of trauma. Yet, as reviewed here, individuals with trauma histories may remember at least some kinds of information with greater clarity than do those without such histories. Moreover, chronic trauma, as experienced by many child maltreatment victims, has physiological and possibly neurological consequences that may affect memory. For such reasons, it is important to differentiate between children with and without trauma histories.

However, given current research, we now propose a third factor, specifically emotion regulation tendencies and related psychopathology. We add this factor as a third type of the second dimension because considerable research points to emotion regulation and associated psychopathology as affecting memory, especially for negative information, but also at times for positive information. And, especially with regard to memory error, it likely is not only the experience of trauma or child maltreatment that matters but also more specifically how that experience affects psychological functioning related to certain types of emotion regulation. In extreme cases, emotion regulation problems may lead to psychopathology, both being subsequent to trauma exposure. Stated another way, the psychological sequelae of childhood trauma will have effects on memory over and above a history of traumatic experiences in childhood. The inclusion of the third factor (emotion regulation/psychopathology) helps us to distinguish effects of trauma from the effects of the consequences of the trauma. Note that when Bremner, Shoebe, and Kilhstrom (2000) compared memory functioning in women with no known abuse histories, women with child sexual abuse histories but no symptoms of posttraumatic stress disorder (PTSD), and women with both child sexual abuse histories and current PTSD, it was only the latter group that showed elevated memory monitoring problems.

This pattern points to possible effects of psychopathology, not of abuse history per se.

Thus, we now expand our second dimension to have three (rather than just two) categories (Table 13.1): (1) typical development (e.g., no significant childhood adversity/no maltreatment or childhood trauma history), with normative emotion regulation strategies; (2) childhood trauma/maltreatment history, with *hyperarousal* emotion regulation tendencies; and (3) childhood trauma/maltreatment history, with *hypoarousal* emotion regulation tendencies. Regarding the first group, by *typical* development, we mean individuals (children or adults) who have not experienced child maltreatment or other serious childhood adversity. This group is usually represented by a nonmaltreated control group in studies on effects of child maltreatment. In attachment theory terms, this group would include a large percentage of securely attached individuals (those who score low in attachment anxiety and low in attachment avoidance). The second group represents a subset of child maltreatment (or child trauma) victims, specifically ones who respond to their adverse childhood experiences with hyperarousal emotion regulation strategies. Individuals who evince reexperiencing and hypervigilance symptoms of PTSD subsequent to child maltreatment would fall in this category. In attachment theory terms, this group would include a large percentage of attachment anxious individuals (individuals who score high in attachment anxiety but low in attachment avoidance). The third group also represents a subset of child maltreatment or child trauma victims, but in this case ones who respond to their adverse childhood experiences with hypoarousal emotion regulation strategies. Individuals who evince avoidance symptoms of PTSD subsequent to child maltreatment would fall in this category. In attachment theory terms, this group would include a large percentage of attachment avoidant individuals (individuals who score low in attachment anxiety but high in attachment avoidance).

TABLE 13.1 Hypothesized Developmental Psychopathology Model of the Effects of Childhood Adversity on Memory

	Type of remembered stimulus[1]	
	Positive/neutral	Negative/traumatic
Maltreated—hyperarousal (including anxiety problems)	−	+
Maltreated—hypoarousal (including avoidance problems)	−	−
Nonabused (controls, typically developing)	0	+

[1]A minus sign (−) indicates less complete or less accurate memory. A plus (+) sign indicates especially vivid or particularly accurate memory. A zero (0) indicates typical memory performance.

Accordingly, when considering the memory development research, it is important to eliminate confusion between, for example, the mundane versus traumatic nature of the stimulus and the background and emotional functioning of the participants. In some studies, the to-be-remembered information is so negatively valenced and high in arousal as to be described as traumatic, but the participants may have no known trauma histories (e.g., Goodman et al., 1997; Merritt et al., 1994). In other studies, the memories under examination may be for neutral or mildly positive information (e.g., fun interactions with adults), but the participants have child maltreatment histories and have reacted to their maltreatment with hyperarousal or hypoarousal emotion regulation tendencies and resulting psychopathology (e.g., Harris et al., in press; McWilliams, Harris, & Goodman, 2014).

Unfortunately, researchers in many studies do not differentiate between child trauma histories and emotion regulation strategies or trauma-related psychopathology, making the aforementioned distinctions impossible to determine and making a comprehensive review of all cells of our classification scheme difficult. Types of childhood emotion regulations strategies should, however, be kept in mind in reading this paper, even when studies do not permit refined analysis separating child maltreatment history and different resulting emotion regulation strategies or trauma-related psychopathology. Given the limited research on some cells and given the significance of certain cells within our classification scheme for understanding the links among child maltreatment, trauma-related psychopathology, and memory, a majority of our review, as well as our main tenets, focuses on the following subset of cells: (1) stimuli are neutral or positive and participants do not have maltreatment or childhood trauma histories; (2) stimuli are positive and participants have maltreatment histories or experienced other childhood traumas; and (3) the stimuli are negative (stressful or trauma related), and the participants have child maltreatment histories or experienced other childhood traumas. When relevant, though, findings from studies falling in the other classification cells are mentioned as well. Also of importance, we differentiate between hyperarousal and hypoarousal emotion regulation strategies and memory performance as possible.

OVERVIEW OF MEMORY DEVELOPMENT

The first cell in our classification scheme concerns typical memory development, in the absence of known child

maltreatment or childhood trauma, and in the absence of trauma-related psychopathology. An understanding of how trauma (such as child maltreatment), or the psychopathology resulting from such, affects memory first requires an understanding of how memory develops under normal conditions. At its most basic level, memory consists of three stages: encoding (i.e., entrance of information into the memory system); storage (i.e., the embedding and upkeep of encoded memory); and retrieval (i.e., accessing stored memories; Alexander et al., 2002; Gordon, Baker-Ward, & Ornstein, 2001). Despite the simplicity of this model, human memory development involves fascinating and complex processes and changes. In this first section, we discuss theories of memory development and relevant empirical findings on the progression of memory functioning across childhood, with a particular focus on autobiographical memory.

Theories of Memory Development

In an important but limited sense, memory development begins in the womb, even before we take our first breaths. Using a habituation paradigm, it can be demonstrated that fetuses remember vibroacoustic stimulations across 10-minute spans beginning at 30 weeks gestational age. By 34 weeks gestational age, fetuses can remember these stimulations over a 4-week period (Dirix, Nijhuis, Jongsma, & Hornstra, 2009). However, habituation is such a basic form of memory that it is evident even in single cell organisms like the amoeba. One should *not* infer from demonstrations such as this that, for humans, prenatal and birth experiences enter consciously accessible autobiographical memory.

Fortunately, theorists have clarified types of memory that have evolved phylogenetically, as well as ontogenetically, in typically developing individuals. These theories refine what is meant by the more general term "memory." The most famous theory in this regard is Endel Tulving's (1985) monohierarchical multimemory systems model. According to this theory, lower organisms and human infants evince procedural memory, such as demonstrated by human fetuses in the vibroacoustic-stimulation habituation task studied by Dirix et al. (2009), mentioned previously. This form of implicit memory is anoetic; that is, such memories are not consciously retrievable. Thus, for the individual, such memories are, in effect, not known, at least not consciously, but instead are primarily expressed behaviorally. Stimulus-response learning, motor memory (e.g., remembering how to aptly turn the corner while riding a bicycle), and habituation are examples of procedural memories. Procedural memories give our memory system a start, and later in development, procedural memories can co-exist with consciously accessible ones.

With brain development, a second form of memory, called semantic memory, emerges, according to Tulving's theory. Such memory is of general knowledge, such as concepts and facts. It is explicit, in the sense that such information can be retrieved into consciousness. However, this type of consciousness is noetic and does not involve consciously recollecting the *context* in which information was learned. It is therefore not autobiographical. We may know that George Washington was the first president of the United States, but not remember when or how we learned this fact. That is, we have lost the memory for the *context* in which the information was engraved in our minds. According to Tulving, young children (up to about 5 or 6 years of age) have procedural and semantic memory. Thus, young children can remember facts and have generalized event representations (e.g., scripts such as what typically occurs at a restaurant, at school, or at bedtime), but not episodic memory.

In Tulving's theory, episodic memory is the most phylogenetically and ontogenetically advanced form of memory. This form of memory permits mental time travel, such that true recollection of unique autobiographical experiences can occur, including the context in which the event happened. Thus, episodic memory permits one of us (GG) to remember (and mentally travel back to the moment of) hearing the news, while sitting in her junior high school home room class, that President John F. Kennedy had been shot, and that she cried and looked over at a classmate from a conservative Republican family, to see if he was, too. Autobiographical memory is a type of episodic memory. (In the previous example, it would also likely be called a flashbulb memory; Brown & Kulik, 1977.) Although Tulving believes that children do not develop episodic memory until about 6 years of age, this view is hotly contested by many developmental psychologists (e.g., Bauer, 2005). A related distinction has been made between familiarity (knowing) and recollection (Jacoby, 1991; Yonelinas, 2002; see Lindsay, Kelley, Yonelinas, & Roediger, 2014), with the idea that familiarity is a fast automatic process whereas recollection is a slower, more deliberative process that emerges in its more adult form around 8 or 9 years of age (e.g., Ghetti & Angelini, 2008; Holliday, 2003).

Although Tulving's theory provides a useful, developmental framework for considering changes in memory during childhood, his ideas regarding memory systems have been challenged in numerous ways. For example, Roediger, Weldon, and Challis (1989) argued for a unitary memory

system in which memory processes but not memory systems vary (see also Burianova, McIntosh, & Grady, 2010). Based on her extensive developmental research, Rovee-Collier (1997) provided empirical support for a unitary memory system beginning in infancy. Moreover, in elicited imitation experiments, older infants and toddlers arguably evidence episodic memory (Bauer, 2014; Bauer, Wenner, Dropik, & Wewerka, 2000; Lukowski et al., 2005; Meltzoff, 1995). Even certain lower animals, such as a subset of birds (e.g., scrub jays), can be shown to have episodic-like memory (Clayton, Salwiczek, & Dickinson, 2007).

These critiques of Tulving's theory are consistent with an alternative formulation, specifically that memory is more associationist in nature. The associationist approach has a long history in philosophy and psychology (e.g., Locke, 1948/1690). In this approach, memory consists of associative networks. With age and experience, the networks become more elaborated (e.g., more intricate, detailed, and connected to other semantic nodes), spreading activation within and across the associative networks becomes faster, and activation becomes more automatic (Howe, 2011). Also according to this approach, semantic networks form our knowledge base, and various encoding, storage, and retrieval processes act on the associative networks. Emotional information is remembered well in large part because it is distinctive. Associationist theories have the advantage of parsimony and considerable scope, but are less developmental in nature, given their emphasis on quantitative growth rather than qualitative changes in memory.

Fuzzy trace theory (FTT) is an alternative theoretical framework for understanding memory development (Brainerd & Reyna, 2001, 2002). According to FTT, children rely more on verbatim memory than do adults, who rely more on gist memory. That is, Fuzzy Trace Theory suggests that young children tend to encode and remember surface features of events (Gordon, et al., 2001; Reyna & Brainerd, 1995). With development, however, individuals increasingly encode and remember the gist (i.e., the semantic/conceptual meaning) of information as well as considerable detail. Although gist memory is said to be less specific than verbatim memory, the former tends to be retained longer. Thus, according to this theory, younger children's memories decay more quickly than those of older children and adults.

Finally, two theories are of particular importance for the development of autobiographical memory. The sociocultural theory, offered by Katherine Nelson and Robyn Fivush (2004), takes inspiration from Vygotsky's ideas (e.g., children's internalization of the mental tools provided by parents) and Nelson's training in developmental psycholinguistics. According to this view, by about 20 months of age, children have the rudimentary language skills to recall small fragments of memory about very recent events. On their own, these very young children cannot structure retrieval of memory for recall; they need an adult's help to communicate memories. However, by 2 years of age, children can recall past events and remember events over relatively long periods of time (Fivush & Hamond, 1989), and by 2.5 to 3 years of age, children can verbally recall prior experiences with some level of coherency (Eisenberg, 1985; Fivush, Gray, & Fromhoff, 1987; Fivush & Schwarzmueller, 1998).

A core and unique part of Nelson and Fivush's proposal is that autobiographical memory emerges, based in important part, on parent–child discussion of past events. Through such discussions, children learn how to structure memory reports and place events on an autobiographical timeline. Individual differences in how children learn this structure, though, also exist. Parents who engage in elaborative discussions with their young children, as opposed to parents who use a more repetitive discussion style, have children who develop earlier and more complete autobiographical memories (Fivush, Haden, & Reese, 2006). Thus, according to Nelson and Fivush, social communication and language play key roles in the development of autobiographical memory.

The last theory of note, the Personalization Theory, was articulated by Howe and Courage (1997). They proposed that autobiographical memory requires development of the self-system, as indexed, for example, by young children's abilities to recognize themselves in the mirror. Without a sense of self, children cannot retain autobiographical information. According to this view, even in the first year of life, children remember previous events but such information does not become autobiographical and is eventually forgotten or inaccessible. Starting between 18 and 24 months of age, an internal representation of the self emerges. This representation provides a knowledge structure around which personally experienced events are organized and retained in memory. In support of their theory, these authors note that the ability to retain autobiographical memories after the age of two is correlated with self-recognition (Courage & Howe, 2010). Subsequent increases in autobiographical memory are explained by a larger knowledge base, greater automaticity of processing, and more developed mnemonic strategy implementation.

Overall, these theories, including those that take a decidedly developmental approach, focus on typically developing children. The theories were not explicitly designed to explain such important topics as memory for

traumatic experiences, effects of acute or chronic child maltreatment on memory, or effects of the onset and continuation of psychopathology in childhood (but see Howe, 2011). It is important nonetheless to keep normal memory development in mind when considering diverse developmental trajectories that may occur as a result of trauma exposure and any subsequent psychopathology. These normal memory frameworks inform theories of developmental psychopathology and memory, and, as such, it is critical to have a sense of the progression of normal memory development.

Empirical Studies of Typical Memory Development

Developmental researchers typically contend that a newborn's brain is not mature enough to consolidate explicit memories that last for years. Whereas some debate children's abilities to develop early episodic memories, many researchers have shown that children have long-term nonverbal memories in infancy (e.g., Bauer, 2005; Fagan, 1970; Meltzoff, 1988; Rovee-Collier, 1999; Rovee-Collier & Cuevas, 2009). These memories, however, tend to have limited retrievability and considerable fragility.

Moreover, many of these early memories cannot be accessed later in life (e.g., older childhood and adulthood), a phenomenon known as infantile amnesia (Courage & Howe, 2010; Reese, 2002, 2009; Peterson, 2002). There are individual differences in the age at which infantile amnesia occurs, and some adults can recall events that date back to when they were 2 years old (Usher & Neisser, 1993). A number of memory development researchers have called for a conceptualization of infantile amnesia as a memory development process, rather than a barrier (Peterson, 2002). According to some authorities, the problem is one of retrieval rather than of complete forgetting (Rovee-Collier, 1997). Despite the fact that we still do not have a definitive explanation for infantile amnesia, we do know that our memory abilities continue to improve throughout childhood and adolescence.

Although even young children can retain an impressive amount of information, overall autobiographical memory performance, including accuracy, number of details recalled, and length of time that self-relevant memories are retained, increases with age (Bauer & Fivush, 2013; Farrar & Goodman, 1992; Gordon, Baker-Ward, & Ornstein, 2001; Howe, 2011). Older children perform better on memory tasks, on average, than younger children—and adults perform better still (Goodman & Reed, 1986; Hudson, 1990). Research links developmental increases in autobiographical memory with social interactions, including parent–child attachment or reminiscing, language abilities, and metacognitive skills (Bauer & Fivush, 2013; Bjorklund, 2011: Chae, Goodman, & Edelstein, 2011; Courage & Howe, 2010; Peterson, 2002). Developmental increases in memory abilities have a number of potential causes. For example, they may be due to increased automaticity (Howe, 2011; Reese, 2009), increased knowledge base (Chi, 1978), increased or improved use of memory strategies (Beuhring & Kee, 1987; Bjorklund, 2011), brain development (Ghetti & Bunge, 2012)—and, most likely, a combination of these factors.

An important driver of development of autobiographical memory concerns increased knowledge about the event or situation to be remembered (Chi, 1978; Mandler, 1984; Nelson, 1986). Repeated events are stored in memory as schemas, or scripts, which are unified sets of mental expectations (organized knowledge bases) about sequences of events that largely play out in the same, routine way each time. School days, medical or dental exams, bedtime routines, and holiday traditions are all examples of events for which a person may have a scripted memory (e.g., First, I put on my PJs, then I brush my teeth, and then I get into bed). Older children and adults tend to have more established scripts than younger children (Nelson, 1986). Information about familiar or well-understood events can be more easily encoded as well as retrieved partially due to the existence of these scripts. As children get older, their knowledge base expands, which likely explains in part their corresponding expansion in memory. (See Brubacher, Roberts, & Powell, 2012, for interviewing children about unique vs. repeated events.)

However, older children's increased script knowledge, and greater ability to use gist memory traces, does not necessarily result in improved memory in all instances. Myles-Worsley et al. (1986) followed children from preschool through third grade and found that the use of scripts for recall can also have drawbacks. Specifically, although the older children remembered more details about the general school-day script, they also misremembered more details about sequences of events that had occurred in school several years before.

Relevant to the development of knowledge base and gist processing, research using the Deese-Roediger-McDermott (DRM) paradigm has revealed reverse developmental trends, where adults and older children often perform worse than younger children (Brainerd, Reyna, & Ceci, 2008). The DRM paradigm requires participants to attempt to remember semantically related lists of words (e.g., dream, pillow, night, bed ...) that are all highly associated with a critical lure (e.g., sleep), which is a word

that does not appear in the list (Roediger, McDermott, & Robinson, 1998: Read, 1996; Otgaar, Peters, & Howe, 2012). Adults frequently create false memories of having heard the critical lure when, in fact, it was never presented (e.g., Gallo, 2006; Roediger et al., 1998). Whereas adults are highly likely to fall for the critical lure on DRM tasks (presumably due to greater gist processing based on their expanded knowledge base), children are much less susceptible to the illusion, at least given the length and types of lists that have been traditionally studied (Brainerd, Reyna, & Forrest, 2002; but see Ghetti, Qin, & Goodman, 2002). This is especially true when young children do not recognize the list items' conceptual relations as readily as do older children and adults or because the lists exceed younger children's working memory capacities (Ghetti et al., 2002). In any case, such reverse developmental trends can also be demonstrated at times in autobiographical memory tasks that rely heavily on knowledge-based inferences (Brainerd et al., 2008).

In summary, a great deal is known about normal memory development, at least for lists of words, everyday routine events, and some aspects of autobiographical memory. We consider typical memory development for stressful events later in this chapter.

EMOTION REGULATION AND MEMORY

Another key concept in our review concerns emotion regulation. We contend that emotion regulation plays an important role both in the expression of psychopathology and in memory functioning and development (see also Richards & Gross, 2000, 2006). A useful starting point is for us to define what we mean by emotion regulation and briefly review how it develops, and what problems in it may arise. Emotion regulation is defined as the "internal and external processes involved in initiating, maintaining, and modulating the occurrence, intensity, and expression of emotions" (Thompson, 1994, p. 27). Precursors to contemporary emotion regulation theories include psychoanalytic theory (Freud, 1909/1995) and classic models of stress and coping (Gross, 1998; Lazarus, 1966). For example, psychoanalytic theories emphasize several types of anxiety regulation, termed ego defenses, which generally focus on avoiding situations that are anxiety-inducing and suppressing the expression of impulses that could result in elevated levels of anxiety (Freud, 1909/1995). For contemporary emotion regulation researchers, the focus has widened to include both conscious and unconscious processes that increase or decrease the experience or expression of either positive or negative emotions (Mayer & Salovey, 1995; Parrott, 1992; Thompson & Goodman, 2010).

Emotion regulation initially develops fairly slowly across development, with advances continuing into adolescence and beyond (Calkins & Bell, 1999; Zeman & Shipman, 1997). In early childhood, emotion regulation largely takes the form of extrinsic, behavioral regulation strategies aimed at reducing negative sensations and increasing positive feelings (Zeman et al., 2006). With age, children begin utilizing more effortful and planful regulation strategies (Lazarus & Folkman, 1984), gain more nuanced understanding of when and how to control emotions (Thompson & Goodman, 2010), and rely more on mentalistic or cognitive tactics (e.g., attentional redirection, cognitive reappraisal) in place of behavioral (e.g., seeking social support, avoidance) strategies.

When considering the role that experiential factors play in children's emerging emotional regulation, caretakers (e.g., parents) serve as particularly important influences, and what children learn from their parents about emotion regulation has long-lasting implications for development (Morris et al., 2011). Parents indirectly influence children's emotion regulation strategies through children's observational learning of their parents' emotional displays (Parke, 1994). Children of parents who display wide ranges of emotions learn a variety of emotional responses in relation to situations that evoke those responses (Denham et al., 1997). Perhaps more evident are the direct effects of parents: Parents who help their children verbally label emotions and empathize with or validate children's emotions have children with more successful emotion regulation strategies. Likewise, parents who actively help children problem solve when dealing with negative emotions (Gottman et al., 1997) have children who tend toward more optimal emotion regulation strategies, such as cognitive reappraisal and seeking social support (Eisenberg & Fabes, 1994). In contrast, parents who react punitively to children's emotions have children who tend toward less optimal emotion regulation strategies, such as avoidance or escape. Parental minimization of children's emotions is also associated with children's greater use of avoidant emotion regulation strategies (Eisenberg, Fabes, Carlo, & Karbon, 1992).

Emotion regulation, in many ways, is intimately tied to children's attachment system. Indeed, Bowlby's (1980) attachment theory has recently been conceptualized in terms of individual differences in emotion regulation strategies (Mikulincer & Shaver, 2007). As Shaver and Mikulincer (2007) noted, "Bowlby (1973, 1980) characterized the stable individual differences in emotion regulation that emerge from prolonged reliance on

particular 'attachment figures,' people who provide either adequate or inadequate protection, safety, support, and guidance concerning emotions and emotion regulation" (p. 446). Research suggests that attachment is best described by the intersection of two orthogonal dimensions, anxiety and avoidance (Fraley & Waller, 1998; Mikulincer & Shaver, 2007; Shaver & Mikulincer, 2003). On the one hand, individuals scoring high on the avoidance dimension are characterized by chronic emotion regulation attempts to deactivate or inhibit attachment-system activation (Edelstein & Shaver, 2004; Fraley, Davis, & Shaver, 1998). To regulate their emotions, these individuals tend to minimize expressions of distress and attempt to hypoactivate their attachment needs (Dozier & Kobak, 1992; Fraley & Shaver, 1997). High scores on the anxiety dimension, on the other hand, appear to reflect hyperactivation of the attachment system, which can also be viewed as an emotion regulation strategy (Cassidy, 2000). Highly anxious individuals are hypervigilant to attachment figures and attachment-related concerns (e.g., Mikulincer, Birnbaum, Woddis, & Nachmias, 2000; Mikulincer, Gillath, & Shaver, 2002) and become easily distressed by separations from attachment figures (Feeney & Noller, 1992; Fraley & Shaver, 1998). These attachment tendencies and the underlying emotion regulation strategies are believed to emerge in childhood and exist across the life span. They can, as well, be combined to delineate the classic attachment styles: Secure adults and secure infants are those who score low on both anxiety and avoidance, dismissing avoidant adults and avoidant infants score low on anxiety and high on avoidance, fearful avoidant adults and disorganized infants score high on both dimensions, and preoccupied adults and anxious-ambivalent infants score low on avoidance and high on anxiety.

We have proposed that emotion regulation strategies, including those associated with the attachment system, are particularly useful in understanding individual differences in autobiographical memory development (Chae, Goodman, & Edelstein, 2010; Goodman, Quas, & Ogle, 2010). Children's mental processing of negative events is especially likely to activate emotion regulation strategies, including the strategies that parents, in effect, impose when dealing with their children's emotions and emotional memories, and strategies that children observationally learn from their parents. For children who themselves are more securely attached, or who have more attachment secure parents, emotion regulation, including that enhanced by the parents' likely support, may facilitate children's attentiveness, storage, rehearsal, or retrieval of negative information. In contrast, children who are more attachment avoidant or have more attachment avoidant parents may demonstrate limited attentional, storage, rehearsal, and/or retrieval processing of negative information, focusing instead on self-protection, their own internal states, and avoidant coping, that is, on the types of emotion regulation strategies that they have learned to use directly or have observed. Children with greater attachment anxiety or with more attachment anxious parents may become fixated on negative emotional information, either ruminating or dwelling on the details of the information without an adequate strategy for alleviating discomfort.

Parental attachment is also associated with parent–child discussion of events, including those that are negatively valenced. For example, more securely attached parents engage in conversations that are more elaborate and emotionally open (Raikes & Thompson, 2008). Such conversations may, in effect, teach children how to interpret and respond to emotional events. Such conversations, as well, help children understand their own emotions and emotion regulation efforts. Parents who self-report as more, rather than less, anxiously attached engage in more explanatory and detailed conversations with their children about stressful information, but also introduce more misinformation (McWilliams, 2014). The latter tendencies may serve to focus children's attention on emotional information but not help children understand that information or regulate their own responses, and may also lead to confusion in children about specific event details. Consistent with Nelson and Fivush's autobiographical memory development theory, such discussions, and the ensuing regulation strategies in children, can affect children's memory (e.g., Reese, 2009; but see Principe, DiPuppo, & Gammel, 2013).

We have also proposed that emotion regulation strategies are characteristic of certain trauma-related psychopathologies, leading to associations of symptoms of such disorders with memory performance. We turn to a multilevel consideration of this proposal next, starting with the effects of maltreatment, including on trauma-related psychopathology symptoms; then briefly describing the psychophysiology of trauma and stress, and relevant neuroscience discoveries; and then delving more deeply into memory for positive and negative events and child trauma research.

EFFECTS OF CHILD MALTREATMENT

Childhood maltreatment, such as physical, emotional, or sexual abuse, can have far-reaching negative effects on development (Cicchetti & Toth, 2005) and increase the

lifetime risk of trauma-related psychopathology, including PTSD, dissociation, and depression (Alley et al., 2015; Berntsen et al., 2012; Eisen et al., 2007; Leeson & Nixon, 2011; Macfie, Cicchetti, & Toth, 2001; Widom, Dumont, & Czaja, 2007). Many effects of childhood trauma, moreover, have biological underpinning or expressions. Accordingly, consideration of behavioral manifestations of the consequences of maltreatment should be accompanied by an evaluation of physiological and neurological concomitants. Moreover, it is always important to keep in mind that child victims are often polyvictimized, such that they experience multiple forms of maltreatment (e.g., neglect and physical abuse). This results in cumulative adversity, increasing the risk of trauma-related psychopathology (e.g., Finkelhor, Ormrod, Turner, & Holt, 2009), emotional dysregulation, and altered physiological response proclivities.

These trauma-related psychopathologies are associated with emotion dysregulation (Shields & Cicchetti, 1998), some of which likely affect autobiographical memory. As mentioned earlier, emotion regulation refers to the approaches taken by an individual to deal with arousing emotions, such as attempting to avoid thinking about traumatic experiences as a means to reduce negative feelings (Bowlby, 1980; Gross & Thompson, 2007; Shields & Cicchetti, 1998; Shipman & Zeman, 2001). It is perhaps not surprising that maltreated children often demonstrate substantial deficits in effective emotion regulation. In maltreating families, there is often a lack of modeling and support; an absence of positive affect; the presence of harsh discipline and negative control; inconsistent discipline; and a lack of parental sensitivity (Shipman & Zeman, 1999, 2001). Maltreating parents also appear to be less understanding of their children's emotional displays and have fewer strategies for effectively helping their children regulate emotions in arousing situations. All of this may lead to emotion regulation problems in maltreated children (Kim & Cicchetti, 2010; Main & George, 1985; Maughan & Cicchetti, 2002; Pears & Fisher, 2005; Robinson et al., 2008), several of which at their extreme manifest in psychopathology. Next we focus on three particularly relevant forms of trauma-related psychopathology.

Trauma-Related Psychopathology

PTSD

After experiencing a traumatic event, a subset of individuals will evince post-traumatic symptoms, and some of these symptoms will be so severe, debilitating, and persistent as to warrant a diagnosis of PTSD. This disorder is characterized by anxiety and memory problems, for example, involuntary intrusions (i.e., flashbacks) of traumatic memories and avoidance of reminders of the precipitating trauma (e.g., Rubin, Bernsten, & Johansen, 2008). Approximately a third of maltreatment victims are diagnosed with PTSD at some point in their lifetime, and many more have elevated levels of PTSD symptoms (Vranceanu, Hobfoll, & Johnson, 2007; Widom, 1999). A child maltreatment history, especially having endured multiple forms of maltreatment, increases the chance of evincing PTSD symptoms (e.g., Bernsten et al., 2012; Finkelhor, Turner, Hamby, & Ormrod, 2011; Finkelhor et al., 2009; Perry & Azad, 1999; Silva et al., 2000; Vranceanu et al., 2007; Widom et al., 2007). As explained by Alley et al. (2015), "The involuntary intrusion of memories may reflect the evolutionarily based need to remember traumatic events in vivid detail so as to avoid the events in the future. The avoidance component of PTSD can be viewed as an (unsuccessful) emotion regulation strategy to limit the processing and memory (including involuntary memory) of traumatic experiences" (pp. 86–87).

Dissociative Tendencies

Individuals who have suffered childhood trauma, including child maltreatment, are also at risk of heightened dissociative tendencies (e.g., Eisen, Goodman, Qin, Davis, & Crayton, 2007; Putnam, 1997). Dissociation is typically conceived as occurring on a continuum from mild detachment to more severe detachment from physical and emotional experience. In the mild form, dissociation is considered a normal process. However, when extreme, it can take the form of a dissociative disorder. These disorders are characterized by a wide range of irregularities in the typically integrated functions of memory, consciousness, and identity, and can result in amnesia, depersonalization, and general confusion (Eisen & Lynn, 2001). Child maltreatment victims may use dissociation to escape negative affect by preventing potentially distressing memories of childhood from reaching cognitive awareness (Becker-Blease, Freyd, & Pears, 2004; Hulette, Fisher, Kim, Ganger, & Landsverk, 2008). Dissociation can therefore also be viewed as an avoidant emotion regulation strategy (but see Giesbrecht, Lynn, Lilienfeld, & Merckelbach, 2008).

Depression

Depression is one of the most commonly diagnosed psychological disorders, and it is often comorbid with PTSD and dissociation. Depression can result from many causes and is not specific to a history of childhood abuse. However,

childhood maltreatment consistently emerges in research as a predictive factor, with younger age at onset of maltreatment being associated with a greater likelihood of depressive symptoms (Jaffee et al., 2002; Kaplow & Widom, 2007; Toth, Manly, & Cicchetti, 1992; Widom et al., 2007). Problems in interpersonal functioning and poor emotion regulation further contribute to and are worsened by depression (Kim & Cicchetti, 2010; Levendosky, Okun, & Parker, 1995). As discussed in greater detail later in this chapter, Williams et al. (2007) found that adult depression that is related to childhood trauma is associated with overgeneral memory, that is, lack of specific recall of events, which Williams and colleagues attribute to avoidance of autobiographical memories. Such avoidance likely reflects an emotion regulation strategy aimed at countering the distress that can arise from remembering negative childhood experiences. Avoidance has been identified as a contributor to depression (e.g., Leventhal, 2008).

Summary

In summary, there are clear reasons to suspect that autobiographical memory for traumatic, stressful, or emotional events is affected by emotion regulation strategies associated with trauma-related psychopathologies, such as PTSD, dissociation, and depression, which are often comorbidly expressed. Before developing this theme further, we turn to consideration of relevant psychophysiology and neuroscience research.

Maltreatment and Psychophysiology

As mentioned, consequences of maltreatment and other childhood traumas are not simply evident in behavioral and emotion regulatory outcomes. Consequences to physiological responses, particularly those that are sensitive to stress exposure, also emerge. Moreover, disruptions or alterations in physiological stress responses themselves have implications for psychopathology, emotion regulation tendencies, and memory. A multilevel approach that takes into account the different domains of consequences and their reciprocal influences is necessary to understand more fully the complexity of the associations among maltreatment, psychopathology, emotion regulation, and memory.

As a starting point to understanding how maltreatment affects physiological response tendencies, it is necessary to describe briefly what is typically meant by physiological reactivity in childhood, a phrase routinely used to describe children's physiological response proclivities. Interest in biological and neurological stress responsive systems in human functioning and behavior has exploded during the past several decades, with a sizeable amount of this work focusing on explaining when and why physiological responses influence social-emotional, cognitive, and mnemonic processes (Hertzman & Boyce, 2010; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 1998; Obradović, 2012; Taylor, Lerner, Sage, Lehman, & Seeman, 2004).

A majority of this work has, as well, focused on specific stress-responsive physiological systems, and how those systems' responses may be altered as a result of trauma exposure, including that due to childhood maltreatment. Systems that have received the largest amount of attention in stress-related research, especially in children, include the locus coeruleus-norepinephrine system or autonomic nervous system (ANS) and the corticotrophin releasing hormone system, more commonly referred to as the hypothalamic-pituitary adrenal (HPA) axis.

Regardless of a history of maltreatment, exposure to stress leads to a host of biological (and behavioral) responses. These responses are necessary, allowing an organism to respond quickly to the stressor. They involve an array of neural structures and target organs, and include preparatory, immediate, and post-exposure biological alterations that foster adaptation to and recovery from the stressor (Chrousos & Gold, 1992; McEwen, 1998; Sapolsky, Romero, & Munck, 2000; Weiner, 1992). Of note, however, the nature and consequence of these responses vary depending on whether the responses emerge as a result of exposure to an acute or unanticipated, single, and short-lasting stressor, or exposure to chronic or repeated threats or stressors (Chrouros & Gold, 1992; Kemeny, 2003; Lupien et al., 2009; McGaugh, 2002; Sapolsky, Romero, & Munck, 2000; Pearlin, Menaghan, Lieberman, & Mullan, 1981). Responses to acute stressors, for instance, are considered both biologically adaptive and appropriate. However, when stressors are chronic or repeated, these acute responses cannot be sustained. Instead, modifications gradually occur. These modifications confer increased risk for a range of adverse physical and mental health outcomes (Essex et al., 2002; Taylor et al., 2004). In addition, exposure to chronic stress can alter subsequent physiological responses to short-term stressors. It is precisely this latter type of exposure and situation that may be particularly common in maltreated children. For them, repeated exposure to maltreatment (rather than a single incident) is often the norm. This likely leads to altered physiological reactivity overall, which then affects the children's (and later adults') ability to mount

a response to novel, acute, and unanticipated challenges. Consideration of the effects of physiological arousal on memory ideally takes into account the type of event that induced the arousal as well as any history of prior stress exposure, and the potential consequences of that exposure on multiple levels of responses and behaviors.

Briefly, regarding the most commonly studied stress-responsive systems, the first is the ANS. Following exposure to a short-term, often unanticipated stressor, both the sympathetic and parasympathetic branches change rapidly. The sympathetic system (SNS) is most closely associated with the classic fight-or-flight response, which prepares an individual for any immediate actions that may be necessary (Berntson, Cacioppo, & Quigley, 1991; Cannon, 1932; Stratakis & Chrousos, 1995).The parasympathetic branch (PNS) may withdraw its regulatory influence, in what is called parasympathetic withdrawal, thereby allowing energy to be diverted in case action is necessary (Berntson, Cacioppo, & Quigley, 1993; Porges, 2007). Once the threat has been eliminated, the PNS then returns to its regulatory function, slowing sympathetic responses and restoring homeostatic control of end-organ functions (Berntson et al., 1993; Kapa, Venkatachalam, & Asirvatham, 2010; Porges, 2007).

The other stress-response system is the HPA axis. It has received the most consistent and widespread attention across studies of physiological stress responses and reactivity (Chrousos, 2009; Dickerson & Kemeny, 2004; Hostinar & Gunnar, 2013). When confronted with a threat, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the release of adrenocorticotropic hormone (ACTH) via the anterior pituitary hormone. ACTH then signals the adrenal cortex to release cortisol, the primary glucocorticoid (GC) in humans (Sapolsky et al., 2000). This heightened cortisol in turn motivates a range of slower-onset excitatory as well as suppressive functions on stress-responses throughout the body.

Our description of stress responses of the ANS and HPA axis focuses, for the most part, on how these systems typically respond to short-term stressors. However, the types of stressors to which many maltreated children are exposed are rarely short-term and may be more appropriately labeled as traumatic. The stressors are also often chronic and unpredictable, which, as mentioned, can lead to long-lasting alterations in how these systems function in general and how they respond to acute stress (Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004). In fact, many different types of chronically adverse environments have been shown to influence both children's general level of arousal when not exposed to stress (i.e., their baseline physiological functioning) as well as their physiological reactivity to acutely stressful events. These environments include not only maltreatment, but also exposure to family conflict, extreme poverty, living in foster care, and premature birth (Erath, El-Sheikh, & Cummings, 2009; Erath, El-Sheikh, Hinnant, & Cummings, 2011; Fisher, Kim, Bruce, & Pears, 2011; Gordis, Ganger, Susman, & Trickett, 2008; Harkness, Stewart, & Wynne-Edwards, 2011; Koss et al., 2013; MacMillan et al., 2009; Ouellet-Morin et al., 2011; Pollak, Vardi, Putzer Bechner, & Curtin; 2005; Scheeringa, Zeanah, Myers, & Putnam, 2004; Sturge-Apple, Davies, Cicchetti, & Manning, 2012). What is important to note about the results across studies is that the directions of the alterations at times vary. Some results are suggestive of hyper-responsiveness, while many other results are suggestive of the opposite, hypo-responsiveness.

A few studies have examined differences in ANS reactivity between children exposed versus not exposed to chronic stress, like maltreatment and family violence. Pollak et al. (2005), for instance, found that physically abused children showed larger SNS reactions to acute, emotionally provocative social stimuli containing expressions of anger and hostility than did nonabused children. Scheeringa et al. (2004) uncovered somewhat similar results in an investigation of young children who had versus had not experienced serious traumas (including both chronic trauma, such as exposure to domestic violence, and singular trauma, such as automobile accidents). This study is of special interest because it concerned memory. Children were asked to recall a pleasant and negative prior experience while their heart rate and PNS responses were monitored. The trauma-exposed children who exhibited high levels of PTSD symptoms exhibited greater arousal (per heart rate and PNS withdrawal) when recounting the negative compared with positive event. The non-trauma exposed children and trauma exposed children without PTSD either responded with decreased arousal or no change in arousal when recounting the negative versus positive prior experience. Other studies, in contrast, have found evidence for hypo-reactivity of the ANS in children growing up in high conflict families and adolescents who have suffered sexual abuse (e.g., Erath et al., 2009, 2011; Gordis et al., 2008).

Unlike the rather small body of work that has examined ANS reactivity in stress-exposed children, a much larger literature exists concerning how chronic stress alters HPA axis functioning, again as mentioned both in response to acute stressors or challenges and in terms of baseline levels of arousal when not exposed to stress, including across

the day (Gunnar & Quevedo, 2007; see Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004, for review). With regard to reactivity, a few studies have reported heightened HPA reactivity in maltreated relative to nonmaltreated children (Harkness, Stewart, & Wynne-Edwards, 2011). Many more, though, have revealed blunted or dampened responses in maltreated and other chronic-stress exposed children (Fisher, Kim, Bruce, & Pears, 2011; Gunnar et al., 2009; Koss et al., 2013; MacMillan et al., 2009; Ouellet-Morin et al., 2011; Sturge-Apple, Davies, Cicchetti, & Manning, 2012).

In terms of atypical basal levels of HPA axis functioning, first, maltreated children seem to have lower baseline levels of HPA axis activation than do non-maltreated children, particularly when morning basal levels are examined (Alink, Cicchetti, Kim, & Rogosch, 2012; King et al., 2001; Loman & Gunnar, 2010). Second, maltreated and other chronically stressed children have been shown to have a flatter rhythm of HPA functioning throughout the day than nonstressed children (Carlson & Earls, 1997; Cicchetti et al., 2010; Dozier et al., 2006; Fisher, Stoolmiller, Gunnar, & Burraston, 2007; Pfeffer, Altemus, Heo, & Jiang, 2007). Of relevance to multilevel approaches to understanding maltreatment, psychopathology, and memory, Cicchetti et al. (2010) found that it was primarily maltreated children who also presented with high depressive or internalizing symptoms who exhibited a flattened HPA axis diurnal response pattern and low morning basal levels of HPA axis activation. Similar findings (i.e., flattened diurnal patterns and low morning basal levels of cortisol) have been reported in studies of children with PTSD following the loss of a parent in the 9/11 attacks (Pfeffer, Altemus, Heo, & Jiang, 2007). Together, research suggests that maltreated children likely have dysregulated patterns of physiological response tendencies relative to nonmaltreated children. This dysregulation is evident in reactions to acute stress in both the ANS and HPA axis, as well as in daily functioning, that is, in basal levels, of the HPA axis. Of note, this dysregulation is reflected at times in heightened reactivity, particularly in younger children who have endured maltreatment or other forms of traumas that induce PTSD symptoms. At other times, and possibly more often in older children and those exposed to chronic, though perhaps slightly lower levels of stress (e.g., harsh parenting), this dysregulation is reflected via dampened physiological reactivity to laboratory stressors, a reduction in diurnal variability of cortisol levels across the day, and lower basal levels of cortisol (but see Bugenthal, Martorell, & Barraza, 2002). This pattern of some children reacting with hyperreactivity and others with hyporeactivity is consistent with our theme of these being important individual differences in children's reactions to trauma, including child maltreatment.

Maltreatment and Neuroscience

As with psychophysiology, there is a growing interest on how trauma may affect neurobiological development and, in turn, how that may affect memory development. Neuroimaging studies of the functional neuroanatomy of autobiographical memory among adults reveal that a core network of left-lateralized regions are involved, including the medial and ventrolateral prefrontal, medial and lateral temporal and retrosplenial/posterior cingulate cortices, the temporoparietal junction, and the cerebellum (Addis, Roberts, & Schacter, 2011; Conway, Pleydell-Pearce, Whitecross, & Sharpe, 2002; Maguire, 2001; Svoboda, McKinnon, & Levine, 2006). In particular, the formation of new autobiographical memories involves the medial temporal lobe, a structure that includes the hippocampus. In addition to these core areas, imaging studies examining the role of emotion and autobiographical memory indicate the additional recruitment of right hemisphere regions (Winston, Strange, O'Doherty, & Dolan, 2002), including regions attributed to emotional processing, such as the amygdala (Greenberg et al., 2005; McGaugh, 2002), the insular cortex (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004), and the orbitofrontal cortex (Rolls, 2002).

Studies relevant to the functional neural development of this core network, in the context of autobiographical memory have begun (see Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Wendelken et al., 2014). Insight can also be gained from research on the physical development of these regions and from research on the adverse effects of trauma on brain development. Although portions of the medial temporal lobe mature relatively early in development (Seress & Abrahám, 2008, for review), other core areas, such as the prefrontal cortex and dentate gyrus, undergo a much more protracted period of development (Bourgeois, 2001; Sowell, Trauner, Gamst, & Jernigan, 2002). Recent research suggests that, although volumetric changes to the hippocampus appear to be limited or absent after the first few years of life (Gogtay et al., 2006), the microstructure of the hippocampus may continue to mature well into middle childhood (Gogtay et al., 2006; Insausti et al., 2010). Moreover, the connections between core structures develop gradually with increasing age (e.g., Lebel & Beaulieu, 2011; Menon, Boyett-Anderson, & Reiss, 2005; Ofen et al., 2007; Schneider, Il'yasov, Hennig, & Martin, 2004). This protracted period of neural development entails a degree of

vulnerability to these core structures, both directly and indirectly. Trauma and/or prolonged stress may disrupt brain development and the neurobiological systems that affect brain maturation and function (Watts-English, Fortson, Gibler, Hopper, & DeBellis, 2006). Because of the prolonged development of some of the core structures that support autobiographical memory, the timing of when trauma occurs may have differential consequences for brain development and function, and subsequently for the development of autobiographical memory (Andersen et al., 2008; Teicher et al., 2003; Teicher et al., 2004; Teicher, Tomodoa, & Andersen, 2006).

Imaging studies of children and adults with a history of trauma, adversity, and/or neglect suggest that trauma-related stress, particularly among those with PTSD symptoms, may adversely affect the volume and function of various brain regions, including some of the core brain structures of the autobiographical memory network such as the hippocampus (Behen et al., 2009; DeBellis et al., 2002; Bremner et al., 2003; Hansen et al., 2010; Tomoda et al., 2009; Tupler & DeBellis, 2006). In general, the decreases in hippocampal volume that have been observed among adults with trauma-related PTSD have generally not been observed among maltreated children (Watts-English et al., 2006; but see Andersen et al., 2008; Teicher et al., 2012). It is possible that the adverse effects of trauma on the hippocampus are not evident until later in development after prolonged exposure to glucocorticoids (Bremner et al., 2003, but see Gilbertson et al., 2002). There is, however, some indication that the hippocampi of children with PTSD symptoms may not function typically (DeBellis, Hooper, Woolley, & Shenk, 2010; Carrion et al., 2010). Garrett et al. (2012), for instance, found that children with posttraumatic stress symptoms showed significantly greater activation in response to emotional facial expressions than did controls in several brain regions, including the amygdala, hippocampus, medial prefrontal cortex, insula, and ventrolateral prefrontal cortex, as well as evincing less activation than controls in the dorsolateral prefrontal cortex.

Dysregulation of the major neurobiological stress response systems, which contribute to and control physiological reactivity (e.g., HPA axis), as a result of trauma may also contribute to alterations in brain structure and metabolic function. Vulnerable brain regions include the amygdala, hippocampus, and prefrontal cortex (Alink, Cicchetti, Kim, & Rogosch, 2012; Chugani et al., 2001; DeBellis, 2005; Hariri & Holmes, 2006; McGowan et al., 2009; Sapolsky, 2000; Van Gaalen, Stenzel-Poore, Holsboer, & Steckler, 2002). Richert et al. (2006) found that children with PTSD symptoms showed a significantly larger volume of gray matter in the middle-inferior and ventral regions of the PFC than did control children. Moreover, decreased volume of gray matter in the dorsal PFC was correlated with increased functional impairment scores. It is difficult to draw clear causal inferences from such studies, however.

Effects of maltreatment, trauma, and psychopathology on the amygdala and hippocampus are of particular importance for memory. However, it is crucial that any evaluation of relevant studies take into account resultant psychopathology. When this is done, it is often the psychopathology rather than maltreatment per se that seems to have the effect. For example, in Bremner et al.'s (2003) research, adults with child maltreatment histories showed reduced hippocampal size, but only in the presence of PTSD. In a longitudinal study of adolescents, Whittle et al. (2013) reported that maltreatment was indirectly associated, through psychopathology, with retarded growth of the left hippocampus and accelerated growth of the left amygdala over time. The authors concluded that psychopathology was a mechanism through which child maltreatment affected brain development, a conclusion consistent with increasing evidence that psychological traumatization is associated with amygdala size and connectivity. For example, Nooner et al. (2013) studied adolescents' self-report of trauma symptoms in relation to functional connectivity of the amygdala. Even mild trauma symptoms seemed to affect brain networks associated with the amygdala. Traumatization may also increase over time, further affecting brain functioning. Herringa et al. (2013) examined brain connectivity in 64 adolescents in a community sample. Childhood maltreatment appeared to alter the regulatory capacity of the brain's fear circuit, leading to increased internalizing symptoms by late adolescence.

Bremner (1999) proposed two distinct acute neurological responses to trauma: hyperarousal and dissociative reponses. These responses are consistent with our proposal that hyperarousal and hypoarousal emotion regulation following maltreatment may both affect memory. Functional magnetic resonance imaging (fMRI) studies have found evidence compatible with Bremner's thesis. Lanius and her colleagues (e.g., Lanius, Bluhm, Lanius, & Pain, 2006) read trauma narratives to soldiers while the soldiers were in the scanner. Relevant to limbic regions, Lanius et al. (2010) reported that a small percentage of the soldiers with PTSD responded with hypoarousal and dissociative distancing; whereas a remaining larger percentage responded with hyperarousal (including flashbacks and other intrusive symptoms). Overall, PTSD patients with a dissociative response to trauma narratives activate neuronal circuitry differently from PTSD patients with a hyperarousal

response. These two reactions are reminiscent of the two dimensions that underlie attachment orientations: attachment anxiety (hyperactivation of the attachment system) and attachment avoidance (hypoactivtaion of the attachment system), and, as will be discussed later, the reactions have implications for individual differences in memory for trauma.

Recently, researchers have uncovered direct relations between activation of the attachment system and brain responses. Normally, secure attachments may help modulate children's emotion regulation, as reflected in amygdala activity and connectivity. Primary caregivers often play a vital role in helping children regulate their emotions. Gee et al. (2014), for instance, examined the effects of caregivers on 4- to 17-year-olds' amygdala regulation. In an emotion identification task, children (but not teenagers) exhibited more mature amygdala-prefrontal connectivity in the presence of maternal stimuli (pictures of their mothers). For maltreated children, who may lack adequate parental succor, caregiver emotional comfort that supports affect regulation via suppression of amygdala activity may occur all too infrequently, whereas fear circuits may be activated chronically. Future research should examine hyperactivation versus hypoactivation of brain circuitry in children as a function of attachment, emotion regulation, and maltreatment history.

In summary, maturation of the core autobiographical memory network varies by neural region, with some core structures maturing early in development and others maturing later. The effect of trauma on brain development and function, therefore, may depend, in part, on the timing and duration of the trauma. Moreover, the dysregulation of neurobiological stress systems may further contribute to alterations in brain structure and function. Neuroscience research indicates two distinct patterns of reactions to trauma, one of hyperarousal and one of hypoarousal. These two patterns may correspond to emotion regulation strategies (e.g., anxiety and avoidance, in attachment theory terms), although additional research is needed to complete our understanding of relations among brain development, emotion regulation, trauma-related psychopathology, and autobiographical memory development.

THEORIES OF TRAUMA AND MEMORY

A number of important theories are relevant to the study of memory in traumatized children. Some of these theories predict that children who suffer trauma will evince particularly accurate memory for negative autobiographical experiences, whereas others predict an impairment in these memories. We first discuss theories that argue for more robust memory and then discuss theories that argue for diminished memory.

Theories of Robust Memory for Negative and Traumatic Experiences

Several basic memory mechanisms and influences underlie theories that propose better memory for trauma-related information, including among traumatized children. For example, the following have been linked empirically to heightened memory for negative and traumatic experiences: arousal combined with negative valence, distinctiveness, knowledge base and expertise, self-schema processing, elaboration, and rehearsal (e.g., see Bjorklund, 2011; Howe, 2006; Howe & Otgaar, 2013; Kensinger, Garoff-Eaton, & Schacter, 2006; McWilliams, Narr, Goodman, Ruiz, & Mendoza, 2013). Traumatic events are likely to leave robust memories because these events are bolstered by activation of neural circuits and structures, such as by the amygdala, specifically evolved to ensure enduring memory for survival threats (Alley et al., 2015; Cordon, Melinder, Goodman, & Edelstein, 2013; Nairne, 2010). Several of the theories of trauma and memory utilize (implicitly or explicitly) such basic memory process notions, but add an analysis specific to traumatic experiences. To provide a sense of relevant theories that propose enhanced memory for negative and traumatic events, we review several theoretical models next.

Christianson's Model

In an important paper, Christianson (1992) reviewed extant research that focused on memory for negative information, which he defined in terms of new, unexpected, and potentially threatening events. The experiments he reviewed were largely laboratory studies, available at that time, concerning adults' memory for one time negatively valenced and highly arousing events or images. He concluded that during stressful or traumatic experiences, attention is riveted to the main stressor (e.g., the snake about to bite, the gun that just appeared in a bank robber's hand), whereas attention to peripheral details is reduced. As a result, memory for the central details of an emotional event should be particularly robust, which was supported by empirical studies even in the laboratory, in contrast to memory for peripheral details, which should be poorer. A two-process model was proposed in which there is first an early, fast, and automatic preattentive process that helps ensure attention to and

encoding of threat information. A second, slower process then takes place that involves evaluation, memory rehearsal, and the like, ensuring consolidation of memory. Christianson's model did not concern individuals with trauma histories or psychopathology. However, it is possible that the acute focus on trauma-related information that Christianson proposed can become, in the face of chronic trauma, hypervigilance to trauma-related experiences, resulting in particularly robust memory for traumatic events (Alexander et al., 2005; Alley et al., 2015; Goodman et al., 2010).

Foa's Fear Network Theory

Foa and her colleagues proposed that traumatized individuals (e.g., those who evince symptoms of PTSD) have fear networks (i.e., semantic/episodic networks of associates) that store trauma-related information and guide both attention and memory. These fear networks result in an overfocus on trauma cues that signal threat to safety or serve as reminders of past threats (Foa, Feske, Murdock, Kozak, & McCarthy, 1991). Accordingly, people who develop PTSD or other anxiety disorders form hyperactivated mental networks of fear-related information. Indeed, this heightened sensitivity to threat cues has been observed in traumatized children and adults (e.g., Dubner & Motta, 1999; McNally et al., 1998; Pollak & Tolley-Schell, 2003). This hypervigilance to threat cues and an elaborated semantic network would be expected to lead to particularly accurate memory for such information.

Survival Processing

Nairne (2010), a cognitive psychologist who is attuned to evolutionary considerations, recently proposed Survival Processing Theory. His framework rests on the idea that humans evolved to prioritize survival-related information with adaptive significance. Given that many traumatic experiences are relevant to current survival as well as to survival in our ancestral past, such experiences should be prioritized in attention and memory. In a series of experiments, Nairne and his colleagues have shown that information that is processed for its survival relevance is remembered better than the same information processed in other ways (Nairne, Pandeirada, & Thompson, 2008; Otgaar, Smeets, & van Bergen, 2010). In regard to traumatized children and adults with chronic threat experiences, survival processing may be activated repeatedly. One would predict, based on Nairne's theory, that such activation should lead to particularly robust memory for traumatic, survival-relevant experiences, with chronic survival processing possibly resulting in even greater attention to and memory for such information.

Theories of Impaired Memory for Negative and Traumatic Experiences

In contrast to the aforementioned theories, several other theories predict inaccurate or incomplete autobiographical memory of trauma experiences. A number of basic cognitive processes can also be brought to bear to predict that traumatized individuals will have holes in their memories or provide inaccurate reports.

Dissociation and Repression

Theories that rely on the notions of dissociation and repression are quite controversial, in part, because they are difficult to test scientifically (e.g., Giesbrecht et al., 2008; Loftus, 1993; Rubin et al., 2008). Nevertheless, such theories try to explain why memories for traumatic experiences can be inaccurate or even lost from conscious access. Van der Kolk and Fisler (1995) proposed that traumatic memories are dissociated and encoded as sensory fragments without cohesion, resulting in incomplete memory traces (see also Putnam, 1997). Freudian theory (Freud, 1909/1995; see also Terr, 1991) serves as a basis for contending that traumatic memories are lost from consciousness due to repression, that is, motivation to avoid reliving the content of painful memories especially those involving self-blame. Although these theories are controversial, there is some support for at least part of their theses. For example, Goodman et al. (2003) found that dissociation predicted lack of memory for childhood sexual abuse. That said, there is also evidence that traumatic memories are particularly coherent and not disjointed (Bernsten et al., 2011; Rubin, 2005). In any case, it is of interest that implicit in these theories is the notion of avoidance of painful memory as an emotion regulation strategy.

Orienting Versus Defensive Responses

Deffenbacher, Bornstein, Penrod, and McGorty (2004) argued that less stressful events are remembered with greater accuracy than are more stressful events. The researchers theorized that less stressful events involve orienting responses (activation mode of processing), whereas highly stressful (e.g., life threatening) events give rise to defensive responses (arousal mode of processing). We interpret defensive responses as a type of emotion regulation strategy put into play when a highly aroused person tries to avoid processing the information, precluding formation of a detailed memory. Much of the research that Deffenbacher et al. (2004) relied upon included individuals who likely score high in avoidant emotion regulation strategies

and who may have a history of exposure to negative events. For instance, eyewitness identification was examined among military personnel (e.g., Morgan et al., 2004), many of whom may have attachment avoidant tendencies to start with. Deffenbacher et al. rightly mention that individual differences likely play an important role in memory for stressful and traumatic events.

Overinterpretation Theory

Windmann and Krüger (1998) proposed a theory that focuses on how trauma can lead to overinterpretation of neutral events as trauma related, resulting in commission errors on memory tasks. Specifically, according to the theory, for the sake of survival, all people are predisposed to be hypervigilant to traumatic material. This is presumably because the amygdala is adapted to respond to such information to help us survive. However, it is further proposed that people who are traumatized overinterpret neutral stimuli as trauma related, which in turn results in commission errors, likely reflecting biased interpretations combined with poor memory monitoring. A signal detection theory approach is needed in research to test this theory, yet such an approach is uncommon in the relevant literature. However, evidence consistent with Windmann and Krüger's theory comes from Pollak et al. (2002) who found that child physical abuse victims exhibited a liberal response bias when perceiving facial expressions of possible anger (but see Pollak & Sinha 2002). Moreover, compared to adults without PTSD, those with PTSD produce more commission errors (e.g., intrusion of unrelated or nonlist words) on DRM false memory tasks, indicating less-rigorous memory monitoring (Bremner et al., 2000; Zoellner et al., 2000).

Proposed Model

We recently proposed a model that sheds light on the contradictory theories and empirical findings concerning child maltreatment and autobiographical memory development. This model reviewed below features emotion regulation in autobiographical memory development especially in relation to memory for negative information (Chae, Goodman, & Edelstein, 2011; Goodman & Melinder, 2007).

In our model, we reinterpret notions such as dissociation and repression as types of emotion regulation strategies. An advantage of considering emotion regulation, over, for example, the concepts of dissociation and repression, is that the former can be more readily measured with psychological instruments and is consistent with several current conceptualizations of coping, emotional competence, and attachment theory (Compas, 1998; Lazarus & Folkman, 1984; Shaver & Mikulincer, 2007; Thompson 1994). Experimental manipulation of emotion regulation results in differential effects on memory (Richards & Gross 2006).

Consistent with Christianson's (1992), Nairne et al.'s (2008), and Windmann and Krüger's (1998) theories, we have proposed that people typically have particularly accurate memories for negative information (e.g., negatively valenced and high arousal events). Based on evolutionary, psychophysiology, and neural (e.g., amygdala) mechanisms, our brains are adapted to prioritize processing of and memory for survival-relevant information. Negative experiences are well retained in memory, because individuals need to recount, consider, and reflect on their pasts to avoid encountering dangerous situations again. Episodic rather than just semantic memory provides humans with a more refined ability than seen in other species to avoid danger through autobiographical memory and therefore to survive. Our reading of the empirical evidence also leads us to agree with Foa et al.'s (1991) formulation of fear networks that underlie traumatized children and adults becoming hypervigilant to trauma and threat cues.

However, consistent with Deffenbacher et al.'s (2004) and Windman and Krüger's (1998) formulations, we also propose that memories may be less robust or less accurate in certain individuals. We interpret their theories and the empirical evidence in terms of emotion regulation strategies. Specifically, there appears to be a subgroup of individuals who are motivated not to think about negative experiences and to employ defensive processes that may dampen, inhibit, or distort trauma memories, which include trying not to think about the trauma, not talking about it with other people, and not rehearsing the information. It is not clear whether such avoidant strategies result in lost memory, but it is likely that they can weaken memories of traumatic events, and perhaps this amounts to lost memory in some cases. Moreover, traumatization can also lead to the overinterpretation of ambiguous situations (including what others might consider positive interpersonal interactions) as trauma related and can lead to poor memory monitoring, consistent with Windman and Krüger's insights. Our ideas are also related to attachment theory, as articulated by Bowlby (1980). As proposed by Shaver and Mikulincer (2007), attachment theory can be interpreted in terms of emotion regulation.

From an evolutionary perspective, the emergence of autobiographical memory has adaptive value; that is, it helps children and adults survive (Chae et al., 2011). For infants and children, survival is highly dependent on

protective caregivers. Threats activate the child's attachment system, ordinarily motivating the child to seek protection from parents. Many negative events are thus attachment related. Children learn to look to their main caretakers (e.g., parents) for both protection from and understanding of such events.

Earlier, we mentioned basic assumptions of attachment theory and of our framework. Here we elaborate on our model, as an example of how emotion regulation affects memory. Attachment styles and associated internal working models likely act as affective and cognitive filters that *regulate emotion* and influence attention to, processing of, and memory for distressing information. Avoidantly attached children whose requests for emotional or physical care have been unattended or rejected may regulate their processing of negative attachment-related information to prevent negative affect associated with memories of attachment loss. When such avoidant (defensive) strategies are activated and negative or otherwise distressing information is not processed, the attachment system remains unactivated. This then eliminates or at least reduces psychological distress, but at the same time it adversely affects memory. Bowlby (1973) referred to this process as defensive exclusion. If these avoidant defenses break down, emotion regulation is disrupted, also adversely affecting memory. In contrast, securely attached children who have developed expectations of responsive and supportive others, and of a worthwhile and loved self, may cope with stress in a nondefensive way, confronting, attending to, and thinking coherently about negative experiences. This would then be more likely to result in accurate and complete autobiographical memory (Alley et al., 2015; Chae et al., 2011).

Parents' own attachment styles should also relate to children's memory of events. Parents' attachment may affect their behaviors toward their children relevant to distressing situations (e.g., preparing their children for stressful events, as possible; providing support or comfort; helping their children process the event afterward). Avoidant parents express that after stressful events they take little time to comfort children and are more likely than secure parents to tell children to just forget about the event and move on, whereas secure parents are more likely to discuss negative life experiences openly and provide children with emotion regulation strategies and understanding that facilitate coherent, accurate memories (Goodman et al., 1997; Jones, Cassidy, & Shaver, 2015). Therefore, children's own and their parents' own attachment orientations result in individual differences in memories of stressful and negative experiences. As verified by studies of adult attachment, the early interactions with parents contribute to emotion regulation strategies that may follow individuals into adulthood (Mikulincer & Shaver, 2007). These strategies thus can influence autobiographical memory in childhood and in adulthood.

We have proposed that this model is helpful for understanding autobiographical memory development in traumatized children, including those who have suffered maltreatment (Alley et al., 2015: Chae et al., 2011). Experiencing repeated adverse childhood events when coupled with avoidant attachment tendencies may result in defensive coping and avoidant emotion-regulation strategies; these then influence later memory duration, detail, distortion, and retrieval style, as well as generating or aggravating psychopathology, such as PTSD (Maughan & Cicchetti, 2002; Mikulincer, Shaver, & Solomon, 2015; Ogle, Rubin, & Siegler, 2014; Williams et al., 2007).

EMPIRICAL STUDIES OF MEMORY IN TRAUMATIZED CHILDREN AND MEMORY FOR STRESSFUL EVENTS IN TYPICAL DEVELOPMENT

Children who experience trauma, such as child maltreatment, especially if at an early age, are at risk of exhibiting delays and nonoptimal developmental trajectories in a number of ways that can affect memory. For example, they may show deficits in performance on verbal recall, attention, and working memory tasks (Bücker et al., 2012). Compared with nontrauma-exposed children, they often score lower on intelligence tests, achieve more limited academic success, and evince disciplinary problems (e.g., Eckenrode, Laird, & Doris, 1993; Eisen et al., 2007; Toth et al., 2011). However, of importance, these deficits may reflect a redirection of cognitive resources, rather than a decrease in overall abilities (Ayoub et al., 2006).

Attention and Encoding in Traumatized Children

Encoding a stimulus is the first step in forming a memory (Gordon et al., 2001). Poor attention to a stimulus during the encoding phase can lead to reduced recall and recognition memory down the line, as well as source-monitoring errors (Naveh-Benjamin, Guez, & Marom, 2003). Contrariwise, intensified attention ordinarily produces particularly detailed and robust memory. Thus, differences in attentional processes (perhaps due to trauma or psychopathology) could provide an explanation for the memory differences in traumatized versus nontraumatized children.

A heightened sensitivity to threat and anger cues, which may optimize encoding of such information, has been observed in maltreated children. Compared with nonmaltreated children, children who have suffered maltreatment show a marked hypervigilance to negative cues (Cicchetti & Ng, 2014; Toth et al., 2011) and a corresponding attentional focus on negative input (Ayoub et al., 2006; Pollak, 2008). For instance, in a selective attention task, physically abused children compared with nonmaltreated children were slower to disengage from angry faces (Pollak & Tolley-Schell, 2003). In addition, among traumatized individuals with PTSD, an increased Stroop interference effect was uncovered for trauma-related material compared with neutral words (e.g., Dubner & Motta, 1999). Such an attentional bias may lead to accurate memory for traumatic or negative information and impaired memory for neutral or positive information (Moradi, Taghavi, Neshat-Doost, Yule, & Dalgleish, 1999, 2000).

Furthermore, a study of 7- to 12-year-olds, some of whom had suffered abuse and some of whom had not, revealed that children who were abused overattended to visual and auditory anger cues (Shackman, Shackman, & Pollak, 2007). The effect was particularly pronounced for visual anger cues when the anger was displayed by the children's abusive mothers, suggesting that this hypervigilance arises in part from familiarity effects and in part as an adaptive response to help maltreated children be vigilant to future threats and violence. For auditory anger cues, although abused children were more attentive to them than nonabused controls, there was not a significant difference between responses to their mothers versus response to cues from strangers, possibly because auditory attention to anger may be more involuntary, or may occur before the child recognizes who the angry party is.

This deployment of additional attention to negative input has a number of potential causes, ones that may have a cumulative effect (Pollak & Tolley-Schell, 2003; Shackman et al., 2007). Children who are maltreated may have learned to attend more to negative situations, such as their abusive parents' anger, because the children associate negative situations with danger, as implied previously. In addition, given that maltreated children attend more to other unfamiliar negative cues than control children, it may also be that maltreated children's attention is caught more by these negative cues. Finally, it may be that maltreated children's attention is related to their attempts at emotion regulation (Toth et al., 2011).

There is also evidence that attentional differences may be due to psychopathology. Children with mood and anxiety disorders, that may or may not be related to maltreatment, show biases for information congruent with the emotional states linked to the disorders (Hankin, Gibb, Abela, & Flory, 2010). For example, youth experiencing depression pay greater attention to sad faces than to happy, neutral, or angry faces. Depressed youth show this preference in comparison to control groups, as well as to youth with anxiety disorders. Conversely, anxious youth pay more attention to angry faces, and youth experiencing comorbid depression and anxiety disorders pay significantly more attention to both sad and angry faces (Hankin et al., 2010). Attentional control, which adults and even children use to some degree to inhibit their attention to irrelevant stimuli and allot attention to important target information (Roderer, Krebs, Schmid, & Roebers, 2012), allows people to extract the most important to-be-remembered information from an event, likely affecting memory. However, given a history of abuse or psychopathology, this selective attention could also bias retention. Rather than there being memory deficits in children and adults who have experienced these problems, it may be that their attentional biases are focused on areas of understandable concern to them (e.g., concerns for safety and for self-esteem, aka, "respect"), and thus what information is encoded and remembered may vary from that of individuals without such concerns. Interpretations can also affect encoding and subsequent memory: Toth et al. (2011) proposed that abused compared with nonabused children are more likely to misinterpret ambiguous actions as negative and have better memories for aggressive stimuli.

It is important to point out, however, that whereas stress at encoding may enhance memory, stress at retrieval may impair it. Although the following study did not include traumatized children, it makes an important contribution by disentangling effects of stress at encoding and stress at retrieval. Specifically, Quas and Lench (2007) examined children's memory for a fear-inducing video clip. The researchers measured the children's physiological stress responses both while the children watched the video (during encoding) and when the children returned to be interviewed a week later (during retrieval). Measuring stress level independently at these two points allows one to separate out the effect of stress on encoding versus retrieval. Additionally, during recall, children were interviewed by either an unsupportive interviewer, increasing the children's stress during that phase, or a supportive interviewer, decreasing their stress during that phase. Children who demonstrated higher levels of stress (based on measured increases in heart rate) during the encoding stage produced fewer incorrect responses when asked to

remember the video. Somewhat conversely, children who were more stressed at retrieval and were questioned by an unsupportive interviewer were more inaccurate in their recall (Quas & Lench, 2007). These findings suggest that stress at encoding may actually be beneficial for memory whereas stress at retrieval may be detrimental.

Basic Associative Memory and Psychopathology

Basic associative memory is a cornerstone of memory development. It is thus of considerable interest to determine if children with trauma histories perform similarly to children without such histories on basic associative memory tasks. As described earlier, the DRM task taps associative memory while at the same time examining false memory for semantic associates. Specifically, as detailed previously, it analyzes whether participants falsely remember that a critical lure was present in a list of semantically related words (Goodman et al., 2011). Recognizing the potential tie between memory of the critical lure and false memory, researchers have utilized the DRM task to see if maltreated compared with nonmaltreated youth show different patterns of memory, when tested either by recall or recognition tests. DRM list studies have thus far not uncovered significant differences in maltreated and nonmaltreated children's false memory of critical lures (Goodman et al., 2011; Howe, Cicchetti, Toth, & Cerrito, 2004; Howe, Toth, & Cicchetti, 2011).

In an important early and relevant study of maltreated children's DRM memory performance, Howe et al. (2004) tested 5- to 12-year-old maltreated children and nonmaltreated controls on the DRM task using standard DRM lists. There were no significant differences in DRM false memory as a function of maltreatment status. Lower socioeconomic status rather than maltreatment predicted memory (see also Howe, Toth, & Cicchetti, 2011). In a related study, Goodman et al. (2011) presented sexually abused adolescents and adults and age-matched nonsexually abused controls with trauma-related DRM lists (e.g., lists with words relevant to such trauma-related topics as sex, rape, fondle), positive lists, negative lists, and neutral lists. Participants with compared to those without child sexual abuse histories did not reveal a difference in recall of the critical lures, regardless of the nature of the DRM list. All participants, however, were more likely to falsely recall the critical lure for child sexual abuse lists and negative lists than for positive lists (Goodman et al., 2011). This pattern could result if the negative lists had tighter semantic associates generally, such that participants were more likely to make associative connections to the nonpresented but highly associated critical lures when the DRM lists were negative.

Despite the similarity in DRM performance for maltreated and nonmaltreated populations generally, researchers have uncovered differences in DRM recall as a function of psychopathology (Goodman et al., 2011; Howe, et al., 2004; Howe, Toth, & Cicchetti, 2011). Goodman et al. (2011) found that adolescents who experienced sexual assault and who also scored high in PTSD symptomology more often falsely recalled the critical lure compared with nonsexually abused individuals and those with child sexual abuse histories who did not score as high in PTSD symptomology. These results are in line with findings showing that maltreated children's tendencies toward memory problems are related to higher levels of psychopathologies.

Memory for Neutral and Positive Events

As mentioned previously, maltreated compared with nonmaltreated children tend to focus on negative input (Ayoub et al., 2006; Pollak, 2008). One could predict that maltreated children's memory would be particularly accurate for negative information, but perhaps less so for positive information, given lack of attention or distorted interpretations of the latter (e.g., Windmann & Krüger, 1998). In two separate studies with maltreated 3- to 6-year-olds, Ayoub et al. (2006) administered the Mean and Nice Interactions Scales. The Mean and Nice Interaction Scales consist of 17 stories with varying interactions, nice, mean, or nice/mean, between either a child and his or her peer (Peer Version) or a child and his or her caretaker (Adult-Child Version). Each story increases in complexity. Children are then asked to recall the story. Recall was coded both for accuracy and complexity of the recalled story, regardless of accuracy. Ayoub et al. (2006) found that, prior to approximately three and a half years of age, maltreated youth had higher recall scores than nonmaltreated youth. After three and a half years of age, however, this difference reversed and maltreated children recalled fewer stories than nonmaltreated children. In further analyzing why these maltreated youth scored lower in overall recall, the researchers discovered that the maltreated youth scored lower primarily on the nice and nice/mean stories. Both maltreated and nonmaltreated youth recalled mean stories at a statistically similar level (Ayoub et al., 2006). Thus, it was not a difference in overall ability to recall that caused the resulting score differences but a difference in recall as it relates to positive stories. Goodman et al. (2010) also found that children with maltreatment histories compared

with those without such histories obtained lower scores in answering specific questions about a positive interaction with a researcher.

Do memory deficits in maltreated children for positive information continue into older elementary age and adolescence, and are the deficits a function of maltreatment or associated psychopathology? McWilliams et al. (2014) asked 9- to 15-year-olds to watch a film clip of a domestic argument or a happy family scene. Approximately half of the children per film clip had maltreatment histories. The children's memory for the film clip was then tested (with IQ scores statistically controlled). Neither a history of maltreatment nor trauma-related psychopathology scores predicted memory for the negative film (the domestic argument). In contrast, higher levels of trauma-related psychopathology (e.g., PTSD, dissociation, depression) were associated with a higher proportion of commission errors in memory about the positive family interaction (see also Young & Widom, 2014).

Building on the previous theme, Chae and colleagues (2011) reported that trauma-related psychopathology, not maltreatment status, predicted memory for a fun interaction, a beanbag game, that occurred during children's stay at a child abuse evaluation center (Chae, Goodman, Eisen, & Qin, 2011). Several days after the children took part in the beanbag game, participants were interviewed, with open-ended, specific, and misleading questions, about the interaction. No significant differences in memory or suggestibility were found between maltreated and nonmaltreated participants, regardless of the children's age. Memory differences were, however, revealed for children with certain symptoms of psychopathology. For instance, although the children's PTSD diagnosis was unrelated to memory accuracy, increased levels of dissociative symptoms were associated with decreased memory performance in children who reported high levels of trauma symptomology. Thus, overall, maltreated children with higher levels of dissociative tendencies and higher trauma symptomology did not perform as well as maltreated children with lower levels of dissociative tendencies and fewer trauma symptoms. It was unclear, however, if the memory errors were due to actual memory deficits or response biases in answering the questions.

Further research is needed to determine if child maltreatment or trauma-related psychopathology is associated with deficient memory performance for positive and neutral events, but not for comparable negative events. Studies such as those previously indicate this as a possible avenue for additional research.

Memory for Stressful and Traumatic Events in Typical Development

Before reviewing research on maltreated children's memory for stressful and traumatic events, it is important to consider typical memory performance in this regard. We do so here rather than earlier as these studies directly set the stage for scientific investigations with child maltreatment samples. The contexts of these studies vary, with some research on children's memory for stressful and traumatic information performed in the laboratory and others taking advantage of stressful or traumatic events that occur in naturalistic contexts.

It is reasonable to ask whether laboratory studies can ever truly recreate the trauma of a highly stressful experience, and whether laboratory-based work is ecologically valid and thus applicable to trauma memories generally (Christianson, 1992; Deffenbacher et al., 2004). Deffenbacher et al. (2004) suggested that the stress experienced under laboratory conditions is fundamentally different from traumatizing or life threatening experiences, such that in the laboratory, stress is actually in the form of arousal, but during life threatening events, a more defensive activation response occurs. The researchers theorized that during a truly threatening situation the defensive activation mode of response is dominant and that this mode leads to impaired memory (but see McKinnon et al., 2015). As noted by Christianson (1992), however, researchers have been quite successful in creating and invoking stressed and emotional reactions in laboratory settings, such as staging crimes and exposing participants to highly distressing photographs. Moreover, a growing number of studies of memory for naturally occurring stressful events, such as invasive medical procedures, although not exactly laboratory based, can still have the advantage of a controlled event that can be documented by researchers, permitting scientific study (e.g., Goodman et al., 1997; Peterson, 2012). These situations arguably provide researchers with data comparable to that obtained from other real-world stressful scenarios while still abiding by ethical requirements.

Research on Stressful Events in Children without Maltreatment Histories

As we articulated earlier, it is important to differentiate, on the one hand, the stressful or traumatic nature of the stimulus or event, and, on the other hand, the traumatic background of the participant. A number of studies have examined memory for traumatic events in children who

have no known histories of prior trauma or maltreatment. Thus, researchers have analyzed these children's memory for traumatic natural occurrences or disasters, such as serious accidents (Peterson, 2012), stressful medical procedures (e.g., Goodman et al., 1991, 1997; Merritt et al., 1994), hurricane-induced floods (Sales, Fivush, Parker, & Bahrick, 2005), and tornadoes (Ackil, Van Abbema, & Bauer, 2003; Bauer, Burch, Van Abbema, & Ackil, 2007). In these studies, children who had personally experienced the event showed detailed and long-standing memories for what happened. Although the researchers' conclusions as to the impact of the distress on the children's memories and the level of recall about the event vary (Goodman et al., 1991; Sales, Fivush, Parker, & Bahrick, 2005), a number of researchers find a positive relation between the stressfulness of the event and the children's later recall. For instance, Ackil et al. (2003) reported that children who had experienced a tornado provided longer and more complete narratives about the traumatic tornado event than nontraumatic events. This relation between the traumatic event and heightened recall persisted over time, in this study across 6 months.

Other researchers have considered how children remember medical procedures, including highly stressful ones (Burgwyn-Bailes, Baker-Ward, Gordon & Ornstein, 2001; Goodman et al., 1997). Goodman et al. (1997) examined children's memory for and suggestibility about a voiding cystourethrogram fluoroscopy (VCUG). Here, the correlation between the stressfulness of the event and children's memory accuracy was related to parental attachment orientations. Thus, whether stress has a negative effect may not be due just to the stressfulness of the event itself but also to the children's background and the context surrounding the distress. Chae et al. (2014) similarly found that children's memory of an inoculation was better for children who had more positive parental representations than children who had less positive parental representations. These findings implicate an important role for parental influence and emotion regulation strategies.

Physiological Stress Responses and Typical Memory

During a stressful event, as mentioned, numerous stress-responsive physiological reactions occur. Such responses, even in children, help them prepare for, respond to, and adapt following stress exposure. These responses, as well, have important implications for attention, encoding, storage, and retrieval of information from memory. To determine a course of action following threat exposure, for example, it is necessary to attend directly to that threat, a process mediated by SNS activation and PNS withdrawal. Enhanced attention should increase encoding. Likewise, high concentrations of glucocorticoid and other relevant receptors that bind to glucocorticoids (Roozendaal et al., 2009) are located in the amygdala and hippocampus, neural regions heavily implicated in attention, encoding, and consolidation, especially of emotional information. Accordingly, when the HPA axis responds to stress exposure, glucocorticoid levels increase, which should, as a result of the activated neural receptors, enhance memory.

An impressive body of scientific work has documented the aforementioned set of links, that is, between physiological response and memory processes, including encoding, consolidation, and declarative memory. A majority of this work has examined memory in adult humans and non-human animals (McGaugh & Roozendaal, 2002; Roozendaal, McEwen, & Chattarji, 2009; Wolf, 2009), but some studies have investigated memory in children.

In adults, tight experimental control has led to well-designed investigations that allow for causal conclusions about the *effects* of physiological arousal on memory. In many studies, stress is induced via a laboratory procedure, such as the Trier social stress test (TSST), which involves giving a surprise speech and solving arithmetic problems in front of a small audience. In other studies, stress is induced via a pharmacological manipulation, such as giving adults a synthetic form of cortisol (e.g., hydrocortisol acetate, dexamethasone). During or after the stress induction procedure (or the completion of a nonarousing control task), participants are exposed to to-be-remembered material, such as pictures, words, stories, or faces depicting emotional or neutral expressions, and not, as described next, autobiographical information (e.g., Cahill & Alkire, 2003; Cahill & McGaugh, 1995; Flint, Bunsey, & Riccio, 2007; Gold & van Buskirk, 1975; Putman, van Honk, Kessels, Mulder, & Koppescharr, 2004; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Smeets, Otgaar, Candel, & Wolf, 2008; Smeets et al., 2009). Findings from studies using these types of experimental designs typically reveal that greater arousal, as indexed via activation of the SNS and HPA axis, or via heart rate (a peripheral measure of ANS activation) at or near the time of encoding, enhances memory (Cohen & Waters, 1985; Lang, Newhagen, & Reeves, 1996; Vrana, Cuthbert, & Lang, 1989; for reviews, see Wolf, 2008, 2009). These effects are particularly pronounced when memory for emotional (primarily negative) information is tested. When stress manipulations are implemented at retrieval, greater physiological arousal,

especially of the HPA axis, inhibits adults' memory (e.g., Wolf, 2009).

In studies with children, the methodologies have diverged substantially from those with adults. First, in developmental studies, of primary interest has been how the amount of stress children experience during a threatening experience relates to their later memory of that experience. Thus, of importance, the to-be-remembered information is the stress-inducing event, thereby tapping autobiographical memory. Second, in many studies with children, stress exposure is not experimentally manipulated; rather all children experience the same event, and individual differences in the magnitude of children's responses to that event are compared with the accuracy and completeness of their memory. Although results from developmental studies are not as consistent as those observed in studies with adults, a number of studies have revealed similar patterns, specifically with regard to arousal at encoding: Physiological arousal is associated with better memory in children, as often observed in adults. For example, Quas and Lench (2007) exposed 5-year-olds to a fear-inducing video while the children's heart rates were monitored. After a week delay, memory for the video was tested. Larger increases in heart rate to the video predicted subsequently better memory for it. Quas et al. (2006) uncovered similar results in a study of children's memory for a fire alarm incident. Specifically, 4- to 8-year-olds' SNS and PNS reactivity was monitored while the children completed a series of laboratory tasks and experienced a brief fire alarm. When asked, shortly afterward, to describe what happened during the alarm, greater SNS-driven arousal was related to better recall. Greater PNS withdrawal, however, was associated with poorer recall, although only in older aged children. When Quas and colleagues (2011, 2012) exposed children, adolescents, and adults to a modified version of the TSST and later tested their memory for details of what occurred, greater HPA axis reactivity during the TSST predicted enhanced recall. This pattern, again, was remarkably similar to that observed in adults (but see Bugental et al., 1992; Chen, Zeltzer, Craske, & Katz, 2000; Merritt et al., 1994; Quas et al., 2014).

Two other developmental findings are important to consider in relation to emotion regulation and memory. One is that, for children, a supportive retrieval context can affect the memory patterns uncovered. Specifically, hints from several investigations suggest that the emotional context at retrieval may influence the type of information that children are able or willing to report about a prior stressful event (Klemfuss, Milojevich, Yim, Rush, & Quas, 2013; Rush et al., 2014). The other is that, while physiological arousal at encoding is often associated with better memory, including in children, among the small number of studies that have tested arousal at retrieval and memory, findings generally reveal negative effects (Nathanson & Saywitz, 2003; Quesada et al., 2012), especially when the interviewer is behaving in a nonsupportive manner (Quas & Lench, 2007). The latter effect, as well, points to the potential significance of emotion regulation at retrieval, especially when children are being asked to recount negative information.

To summarize, research with adults consistently reveals beneficial effects on memory of physiological arousal at encoding and negative effects on memory of such arousal at retrieval, especially when arousal is indexed by HPA axis activation, with these effects emerging largely as a result of changes in levels of circulating cortisol activating neural regions (e.g., in the limbic system) heavily implicated in attention, emotional processing, encoding, and consolidation of information. In children, greater physiological arousal at encoding is at times associated with enhanced memory for stressful to-be-remembered experiences, although few studies have utilized the types of tight experimental manipulations of stress and content of to-be-remembered information as that employed in studies with adults, which would enable clearer interpretation of findings and causal conclusions to be drawn. Greater physiological arousal at retrieval is often predictive of poorer memory in children, or perhaps a reduced willingness to answer questions correctly.

Memory for Stressful and Traumatic Events in Child Maltreatment Victims

Recognizing that differences in the traumatic nature of information to be recalled can affect memory performance, as can the traumatic nature of the children's personal histories, researchers have analyzed maltreated children's recall of traumatic events that the children personally experienced (e.g., Greenhoot, McCloskey, & Glisky, 2005; Melinder, Baugerud, Ovenstad, & Goodman, 2013). Although any discussion of memory for traumatic events requires an acknowledgment of the potential effect stress may have on motivation to report what occurred and other possible effects of distress on retrieval of memories, there is evidence within research on child maltreatment victims' recall of traumatic events that stress benefits recall. Moreover, although some participants fail to reveal prior documented abuse histories (Greenhoot et al., 2005), researchers have found that, when maltreated individuals do reveal prior abuse, they are relatively accurate in remembering the traumatic event (Alexander et al., 2005).

For instance, Alexander et al. (2005) interviewed older children and young adults about sexual abuse they experienced over a decade previously. Overall, the victims demonstrated fairly accurate recall of the abuse (accuracy was determined based on comparisons of the later reports to details in the original case files). However, and as was hypothesized, individual differences in psychopathology significantly predicted to the victims' recall. Individuals who reported their prior sexual abuse as their most traumatic experience and who revealed higher PTSD symptomology had better recall for their prior documented abuse experiences. Individuals with higher frequency of abuse, however, had higher rates of omission in their recall of their prior assaults. There are a number of potential explanations for this difference. First, as the authors note, this may be due in part to schematization of the memory where individuals who have experienced a higher frequency of abuse have generalized these memories due to the events' reoccurrence. Second, this decreased recall may not be an issue of the participants' inability to recall the events but, instead, of participants' hesitancy to report their abuse, particularly where this abuse has occurred quite frequently.

Maltreated children's memory for traumatic events other than the abuse also shows little in the way of consistent relations to the prior maltreatment. Two related studies, for instance, examined maltreated and nonmaltreated children's memory of an anogenital examination (Eisen et al., 2002) and/or venipuncture (i.e., blood draw; Eisen et al., 2007). In both studies, maltreatment status overall was unrelated to children's memory performance. However, in the 2007 study that included memory for an anogenital examination and venipuncture, the sexual and physical abuse victims actually performed better than others on a few of the memory measures. Of interest, sexual abuse and physical abuse victims actually had the fewest omission errors as to abuse-related questions.

Both Eisen et al. (2002) and Eisen et al. (2007) also found relations between certain psychopathologies and children's memory. In the Eisen et al. (2002) study, the children's GAF (psychological functioning/adjustment) ratings predicted the errors in memory interviews. Surprisingly, dissociation did not predict memory errors in this study. However, in the Eisen et al. (2007) project, the researchers found that dissociation was predictive of memory performance when one considered the level of children's physiological stress about the event and their self-reported trauma symptoms. Specifically, highly stressed children with higher dissociation and trauma symptom scores produced the most memory errors and were the most suggestible of the children tested. For the latter study, no connection between PTSD diagnosis and memory was found.

Research analyzing traumatized children's memory for stressful events thus reveals similar patterns to that found in memory for nonstressful events. Maltreatment itself appears to play a role in memory for trauma-related information in terms of enhancing memory when the type of trauma fits the type of event to be remembered, perhaps due to biased attention and/or greater knowledge (as seen for the sexually abused children in the Eisen et al., 2007, study). Further memory differences between abused and nonabused children seem to be primarily associated with factors such as emotion regulation and psychopathology. That said, the previously outlined research does not specifically reveal the source of these differences.

Maltreatment, Physiological Reactivity, and Memory

As reviewed earlier in this chapter, physiological reactivity and basal arousal vary between maltreated and nonmaltreated children. Given that reactivity has implications for memory, multi-level models of trauma, psychopathology, and memory should consider the extent to which possible differences between maltreated and nonmaltreated children's memory are linked to underlying variations between the groups in physiological responsivity. Precisely how these effects may play out is difficult to ascertain, and little research has actually examined these complex links.

When considering the links among maltreatment, reactivity, and memory, one possibility is that, following stress exposure, maltreated children will exhibit poorer memory for emotionally laden information than nonmaltreated children. This possibility stems from evidence that chronic exposure to maltreatment often reduces children's physiological reactivity, and evidence that heightened physiological reactivity near encoding, particularly of the HPA axis, enhances memory, theoretically as a result of activation of neural regions (e.g., the hippocampus) heavily involved in memory encoding and transfer of information to long-term storage. As such, maltreated children's hypothesized poor memory under stress would not be due to active attempts to avoid emotional information or potential difficulty understanding emotional events, but instead, would be due to reduced activation of memory-dependent neural regions implicated in basic memory processes.

Despite this possibility, as already mentioned, studies have not revealed differences between maltreated (or other stress-exposed groups) and nonmaltreated children in arousal and memory, including between stress-exposed

and nonexposed children. Nor have studies found any links between arousal and memory in maltreated children specifically. For instance, in an investigation described earlier, Scheeringa et al. (2004) collected heart rate and PNS responses in young children who had and had not been exposed to traumas while they were recounting prior experiences. The researchers coded children's descriptions for accuracy and compared the children's accuracy to their physiological responses. No significant differences were uncovered in any of the groups (traumatized with and without PTSD, nontraumatized) in physiological responses between children who were more versus less accurate in their memory reports. Likewise, Eisen et al. (2007) did not find any significant associations between maltreated children's heart rate while undergoing an anogenital medical exam that occurred while they were in-patients in an evaluation facility and their later memory for the exam.

However, studies have rarely measured maltreated children's HPA axis responses in relation to memory (but see Eisen et al., 2007). In adults, consistent evidence has been uncovered linking physiological reactivity (especially as driven by the HPA axis) and memory. The evidence for this link is stronger when memory for well-validated material is tested rather than when memory for prior personal experiences, including autobiographical memory, is tested, though in the studies with adults, none has relied on a traumatized (e.g., formerly maltreated in childhood) sample or compared performance between traumatized and nontraumatized adults. Future research is needed to examine, in a much more comprehensive manner, whether the effects of stress on memory vary between maltreated and nonmaltreated children, or between other samples of trauma-exposed individuals and nontrauma-exposed individuals. If any such difference emerges, it will be critical as well to test whether differences in physiological reactivity explain or simply correlate with evident trends.

A few other studies have examined how chronic stress and concomitant physiological dysregulation relate to general cognitive and memory abilities, as compared with autobiographical memories. Chronically high and low levels of cortisol have been linked to deficits in cognitive functioning and to poor performance on standardized memory tasks (Blair, Granger, & Razza, 2005; Cicchetti et al. 2010; Lupien, King, Meaney, & McEwen, 2001). For instance, in young children enrolled in a preschool program for low-income families as well as young children who spent (in infancy) a longer time in neonatal intensive care units, higher baseline cortisol levels predict poorer performance on cognitive measures (Blair, Granger, & Razza, 2005; Bugental et al., 2010). (Note: steroid [cortisol] inoculations are often given to women in preterm labor to develop the neonates' lungs, which while meant to help premature infants survive may also have long term effects on their HPA axis function and mental health; e.g., Kahlife et al., 2013.) At the same time, particularly low levels of cortisol, at least among chronically neglected or emotionally abused children, are related to more errors on a declarative memory task (Cicchetti et al., 2010). These studies are largely correlational, however, and thus causal inference is precluded. Moreover, the extent to which these outcomes relate to children's autobiographical and episodic memory is not entirely clear. Thus, although maltreated children may exhibit dysregulated physiological responses and may evidence cognitive deficits on certain standardized tests of memory, it is not known from extant research whether or why these deficits would spread to autobiographical and episodic memory and how these may relate to psychopathology.

Maltreatment and Overgeneral Memory

Psychopathology and childhood adversity seem to influence individuals' reporting of their autobiographical memories, sometimes with striking, but not fully understood, effects. Here, we discuss one specific autobiographical memory propensity that has been associated with childhood trauma, overgeneral memory (OGM), as an example of how emotion regulation and psychopathology may affect memory. This area of study also reveals complexities in pinpointing effects and even in replicating findings.

Williams and Broadbent discovered OGM while studying autobiographical memory in suicidal versus nondepressed adults. When asked to recount specific autobiographical memories in response to cue words, adults who had recently attempted suicide (i.e., parasuicidal) showed a pattern of retrieval deficits (Williams & Broadbent, 1986). Rather than retrieving specific memories, which are defined as memories for events that lasted one day or less and happened at a particular time and place (e.g., Having lunch with my friend on Saturday), the parasuicidal adults, as compared with a control group, provided general categorical memories (e.g., Every time I have lunch with my friend) or extended memories (e.g., My trip to England last year). Follow-up studies have repeatedly supported the presence of OGM in depressed patients (e.g., Brittlebank, Scott, Williams, & Ferrier, 1993; Swales, Williams, & Wood, 2001; Valentino, Toth, & Cicchetti, 2009). In both currently depressed people and those who were previously but are not currently depressed, OGM is

predictive of future recurrence of depression, increased feelings of hopelessness, poorer social relations, and impaired social problem-solving (Brittlebank et al., 1993; Sumner et al., 2010; Swales et al., 2001).

Further research has shown links between other psychopathologies and OGM. McNally, Lasko, Macklin, and Pitman (1995) found OGM in Vietnam veterans with PTSD, a link that has subsequently been shown in other samples of people experiencing PTSD (Schonfeld, Ehlers, Bollinghaus, & Rief, 2007). OGM has also been linked to borderline personality disorder, acute stress disorder, suicidality without depressive history, and early life trauma, in particular child abuse (Swales et al., 2001).

Several studies of OGM in depressed, traumatized, and PTSD individuals have uncovered their particular difficulty in retrieving specific positive memories. However, some studies have found that these populations do not have any more trouble than control groups at retrieving negative memories (Brittlebank et al., 1993; McNally et al., 1995; Swales et al., 2001, but see Williams, 2006). This pattern is reminiscent of that described earlier in which trauma-related psychopathy subsequent to maltreatment was associated with memory deficits for positive but not negative autobiographical experiences.

Williams (2006) proposed the CaRFAX (Capture and Rumination, Functional Avoidance, and Executive Control Dysfunction) model to explain OGM. Capture and Rumination refers to the way people who evince OGM tend to have certain negative memories or thoughts that capture their attention, as well as their mental and emotional resources. It was proposed that this step then leads to Functional Avoidance: a conscious attempt by the individuals to evade the negative feelings associated with particular specific memories so as to regulate arousal and affect, an emotion regulation process, resulting in truncated retrieval. Finally, the CaRFAX model proposes that individuals with OMG experience Executive Control Dysfunction, which helps explain the necessity of the avoidant strategies: The distress and other problems caused by their psychopathologies may leave people with reduced executive control, so that avoiding capture by distressing thoughts is much harder. Overall, OGM appears to reflect a maladaptive emotional regulation strategy related to traumatic events or thoughts that is difficult for people with histories of childhood adversity to overcome, at least under the conditions of timed tests (Bunnell & Greenhoot, 2012; Goodman et al., 2010).

Given the high rates of comorbidity between many of these disorders and the intercorrelated variables (e.g., childhood trauma and later depressed mood) involved, it is difficult to determine precisely how the various factors contribute to OGM, and under what conditions OGM is likely to arise. Of special interest, there have been conflicting findings as to whether OGM is primarily predicted by psychopathology, often depression, or instead by a prior childhood trauma, such as child sexual abuse (e.g., Kuyken & Brewin, 1995; Orbach, Lamb, Sternberg, Williams, & Dawud-Noursi, 2001; see Valentino, Toth, & Cicchetti, 2009, for a review). A 2010 meta-analysis by Sumner, Griffith, and Mineka found small but significant predictive values for OGM of depression, solidifying a link between depression and overgeneral memories, particularly in present clinical samples. However, many studies have also uncovered evidence that childhood trauma history is related to OGM (Aglan et al., 2010; Kuyken & Brewin, 1995; McNally et al., 2006; Valentino et al., 2009).

Valentino et al. (2009) suggest that this split in the literature may be due in part to the difficulty in measuring the amount of trauma that a person has experienced during his or her life, and how severe his or her traumas have been. In analyzing OGM in groups of abused, neglected, and maltreated children, Valentino et al. (2009) reported that the children in the abuse group had higher levels of OGM than the children in the neglected or nonmaltreated groups. The neglect and nonmaltreatment groups did not differ significantly in OGM. It was postulated that, although the neglected and abused children had all experienced maltreatment, the abused children suffered specific events and memories in ways that neglected children did not, and thus the neglected children would not have memories that they needed to avoid in the same way as the abused group. Valentino (2011) also suggests that the timing and severity of traumatic events may result in later OGM and psychopathologies. Of note, in Valentino et al.'s (2009) study, OGM was not mediated by depression in the abused sample, suggesting that trauma leads to OGM regardless of depression.

In a study by Stange, Hamlat, Hamilton, Abramson, and Alloy (2013), the researchers found that in Caucasian adolescents with OGM, emotional maltreatment predicted increases in depression more than it did for African American adolescents with OGM. Early differences in socialization may put groups at different levels of risk based on their upbringing. Caucasian parents tend to talk to their children about specific past events more than African American parents do, so there is a possibility that OGM is less predictive of future psychopathology in an African American sample just based on these varying styles of socialization. If nonspecific memory is already in place as a normal style of memory development instead

of a protective strategy, we would not expect it to have the same outcome as in a group that is more inclined toward specific memories normally. These variations have been noted and explored in other ethnic groups as well (see Valentino, 2011, for a review). Further research is necessary to determine what role ethnicity, psychopathology, and prior trauma play in resulting OGM.

Moreover, discrepancies in the OGM literature might be explained by considering the two responses to childhood trauma discussed earlier in this chapter, specifically a hyperarousal and hypoarousal response (Harris et al., in press). One would expect that use of functional avoidance as an emotion regulation strategy would be associated with a hypoarousal response to trauma, for example, perhaps to a general avoidant coping tendency (e.g., Bunnell & Greenhoot, 2012). In contrast, a hyperarousal response to trauma might well lead to specific memory retrieval rather than OGM (see Ogle et al., 2008, for review).

Translational Issues

As is evident from our review, multiple practical implications emerge when attempting to understand how well maltreated children, particularly those who exhibit significant impairments in emotion regulation, can remember and recount prior experiences, including those experiences that were and were not stressful or traumatic. Two domains, though, stand out as being especially important, with the understanding that what children remember about prior experiences, how they communicate those memories, and the effects of those memories on the children's current and ongoing functioning are all intertwined.

The first domain within which the research must be translated and understood is that involving clinical interventions and treatments for maltreated and trauma-exposed children. Clinicians and therapists are routinely faced with the need to interact with and solicit information from children about not only the children's experiences, but also their thoughts and interpretations of those experiences. Clinicians need to be aware of when trauma and stress may affect children's reporting of their experiences, and when it may not. That is, stress and trauma may not affect children's overall memory, but may instead shape the content of what is recalled (Howe, 2011; Klemfuss et al., 2013) and how children come to understand their experiences. Clinicians also, though, need to be well versed in the different ways memory may be affected. Moreover, as we outlined early in this chapter, it is incredibly useful to distinguish the type of information being recalled, or as we described, the type of stimulus (traumatic or not); children's backgrounds (maltreated or not) in relation to children's type of emotion regulation and psychopathology. Within this factorial design, which cell one is considering may shape the interpretations and conclusions that can be drawn about children's memory reports. Which cell, as well, likely shapes how children talk about and recount specific experiences. Accordingly, knowing which cell is being targeted can help clinicians guide their questions and interpret children's responses.

The second domain is the legal system. Children who suffer or witness maltreatment or other traumatic events are often interviewed by child protection and legal authorities (e.g., social workers, law enforcement officers, attorneys, judges) about both positive and negative events in their lives. It is vital that such authorities become aware of the many factors that can affect children's accuracy and completeness of report. Children with trauma backgrounds who have experienced or witnessed crime may attempt to regulate their emotions by truncating recall, yet child forensic interview protocols largely require free recall reports. Because relatively few studies have been conducted on the accuracy of maltreated and traumatized children's memory, there is still much to learn to ensure interview protocols used in child forensic interview centers optimally tap traumatized children's abilities and willingness to report their memories and resist false suggestions.

Conclusions and Future Directions

Whereas differences in memory between children who have experienced trauma and those who have not have been detected, the research thus far primarily supports a hypothesis that individual differences in psychopathology and emotion regulation, more so than maltreatment per se, play important roles. Maltreated children often show comparable memory performance to that of nonmaltreated children (Goodman et al., 2011; Howe, Toth, & Cicchetti, 2011; Howe et al., 2004). Additionally, child maltreatment history and resulting psychopathology do not necessarily result in memory deficits but may in fact improve retention, particularly for trauma-related events. For instance, individuals who evince PTSD symptomology have particularly accurate recall for the events that they report are highly traumatic (Alexander et al., 2005; McKinnon et al., 2015). Despite these general patterns, additional research is necessary in a number of areas.

First, additional research is needed into the effects of individual differences on children's memories for negative versus positive information, distinguishing between valence and arousal (Kensinger et al., 2006). Traumatized

children as a group, compared with children without trauma histories, have a number of characteristics that potentially could result in memory deficits or memory advantages, such as their attachment orientation, attentional focus, and emotion regulation tendencies. Whereas in this paper, we have argued that individual differences in emotion regulation and psychopathology, and not as much in trauma background itself, predict important aspects of memory error and performance, additional research is needed to support or refute this hypothesis. Research is also needed to explain protective factors that may exist that preserve memory functioning in spite of trauma. Such investigations should include longitudinal research on children's memories for traumatic events and positive events.

Second, although attachment orientations have been repeatedly shown to relate to memory accuracy and completeness for stressful and/or attachment-related events (Edelstein et al., 2005), further research is needed into the exact mechanisms involved, such as parental representations (Valentino et al., 2008) and parent–child communication (McWilliams, 2014) that may result in memory differences. In addition, neuroscience studies that show hyperarousal compared with hypoarousal (e.g., in PTSD response to trauma narratives) would profit from attention to the roles of attachment orientations of research participants, considering the separable dimensions of attachment anxiety and attachment avoidance. Overall, several discrepancies in the trauma and memory research literature may be resolved, at least in part, by considering the distinction between a hyperarousal and hypoarousal response.

Third, additional research is needed on how to bolster and improve children's memory even in the face of psychopathology, including how to increase resistance to false suggestion and reduce memory monitoring errors. For instance, Lyon and Dorado (2008) showed that when maltreated children take a truth-telling oath, their rates of true disclosures increased. These small social contracts and changes in approach can perhaps make a large difference in the way maltreated children recall their memories to others. Such changes have the potential to make a difference in the legal arena and can help alleviate the concerns raised regarding the types of suggestibility that can lead to memory errors. In the study of trauma and memory, socioemotional and cognitive factors must both be considered to understand and improve children's memory reports.

Finally, the burgeoning field of research analyzing the connections between neuroscience, psychophysiology, and children's memory continues to be a necessary area of focus. As noted previously, this includes research into whether, and if so how, neurobiological effects of trauma influence the developmental trajectory of maltreated children's memory functioning. A richer understanding of these phenomena can help practitioners provide better services to traumatized children and adults who are asked to recall their pasts.

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CHAPTER 14

Attention and Impulsivity

JOEL T. NIGG

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INTRODUCTION

Few abilities are as important for success in contemporary societies as the ability to exercise self-control. Conversely, few developmental difficulties generate as much controversy and concern in our society as problems with inattention and impulsivity.

Self-control and self-regulation (defined momentarily) develop, and go awry, via the synergistic interplay of multiple psychological, neural, behavioral, and social systems, including bottom-up reactive processes (i.e., behavioral inhibition and approach, in turn directly influencing arousal regulation), top-down effortful control or executive functions, language development, and dynamic interaction with socialization processes (e.g., parent–child relationships and learning opportunities) in infancy, preschool, and the school-age years. In the prior edition of this volume, my coauthors and I (Nigg, Hinshaw, & Huang-Pollack, 2006) emphasized the interplay of socialization and interior dynamics of the child's cognitive, language, and emotional development in the gradual unfolding of self-regulation, as well as in the breakdowns that emerge into attention-deficit/hyperactivity disorder (ADHD) (APA, 2013).

This chapter therefore takes a somewhat different tack. It does not recapitulate the review of socialization and the role of language. Instead, after noting basic framing concepts similar to those described by Nigg et al., including an updated account of clinical features and history, it elaborates a two-process conceptualization of self-control of attention and impulse. This chapter is therefore entirely

[1]Color versions of Figures 14.1, 14.2, 14.4, 14.5, 14.6, 14.11 and 14.13 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

updated from the prior edition of this handbook. It outlines how this basic model can be used both to understand disorders like ADHD and to guide new research.

In the process, the chapter considers the formal constructs of attention and impulse control, outlining their development, and pointing out illustrative recent findings related to ADHD that help the reader understand normal and abnormal development of these abilities. The review is selective and heuristic, highlighting recent developments, selecting classic findings, and pointing readers to meta-analyses and comprehensive recent reviews on key component literatures for further study.

Developmental changes are notable throughout the life span, including infancy and young adulthood (Nigg et al., 2005) and old age (Hasher & Zacks, 1988; Zacks & Hasher, 1994). However, data on ADHD in later life are sparse; normative cognitive aging is beyond the scope of this chapter and well reviewed elsewhere (Park, 2012; Spreng, Wojtowicz, & Grady, 2010). This chapter therefore largely bypasses discussion of cognitive decline of attention or impulse control in later adulthood.

Throughout, in keeping with the developmental psychopathology perspective of multiple levels of analysis (Cicchetti & Dawson, 2002), the essay considers multiple perspectives. While emphasizing the psychological and neural levels of analysis, careful note is taken of considerations relevant to the genetic and socialization contexts, all with an eye on development.

Self-Regulation and ADHD

In the normative domain, one can invoke the concept of *self-control* (implying *deliberate* control or regulation of thoughts, behavior, and emotions) or the even broader domain of *self-regulation,* encompassing both deliberate self-control and involuntary regulatory processes related to attention, mental ideation, behavior, and emotion. Because in most research the two constructs are not operationally distinguished, the text herein refers to self-regulation except when the data clearly pertain only to self-control. The wide array of positive and negative life outcomes that are related to self-regulatory abilities includes physical health, mental health disorders, substance abuse, academic achievement, school readiness, learning, peer relations, development of conscience, resilience to adversity, and even mortality and longevity (Blair & Razza, 2007; Calkins & Keane, 2009; Clausen, 1993; Gorenstein & Newman, 1980; Iacono, Malone, & McGue, 2008; Kern, 2008; Krueger et al., 2002; Krueger, Markon, Patrick, & Iacono, 2005; Moffitt et al., 2011; Nigg, 2006a; Wood, Rijsdijk, Asherson, & Kuntsi, 2009; Young et al., 2009). The importance of adaptive and maladaptive self-regulation and its relevance to life outcome therefore is compelling.

In the maladaptive domain, self-regulation broadly defined is so fundamental that it influences almost all psychopathology to some extent, from depression, to aggression, to ADHD (Rudolph, Troop-Gordon, & Llewellyn, 2013). This includes poor regulation of attention, planning, foresight, and working memory (inattention) and poor regulation of decision making, motor response, speech, and emotional expression (impulsivity). Mirsky and Duncan (2001) listed 17 psychiatric and neurological conditions associated with disordered attention, including schizophrenia, autism, fetal alcohol syndrome, closed-head injury, and narcolepsy. Crucially, however, the term *attention* connotes multiple functions; not all such functions are equally affected across these various conditions.

Impulse control likewise is multiply defined and multicomponential (Nigg, 2000; Whiteside & Lynam, 2003) and appears in a range of conditions, of which ADHD may be the most prominent but is hardly the sole exemplar. Antisocial behaviors (including conduct problems and psychopathy), eating disorders, personality disorders (notably borderline personality disorder and antisocial personality disorder), substance abuse disorders, tic disorders, obsessive-compulsive disorder, bipolar disorder, and pathological gambling are only some of the psychopathologies readily associated with serious maldevelopment of impulse control (Coles, 1997). Many of these are syndromes primarily observed in adulthood, and their relation to childhood impulsivity is largely unstudied. Nonetheless, clearly the correspondence is not one-to-one between the topic of disorders of attention and impulse control and the clinical syndrome of ADHD.

Indeed, this fundamental quality of underlying shared dimensionality is part of the reason that there is extensive overlap between ADHD and aggression and some overlap between ADHD and mood problems such as irritability (Shaw, Stringaris, Nigg, & Leibenluft, 2014), as well as to a lesser extent mood disorders like depression. That is, the ability to regulate impulse and attention is related to fundamental human capabilities that cut across descriptive categories of psychopathology. To constrain the scope of discussion, however, and because aggression and mood problems are discussed in other chapters, this chapter's emphasis is ADHD, a syndrome which is paradigmatic of problems in the domain of self-regulation. Readers may bear in mind that the underlying regulatory abilities discussed herein are likely related across conditions other than ADHD.

At the same time, ADHD affords certain unique considerations. Most salient is the perspective taken in *DSM-5*

(APA, 2013), that ADHD is a neurodevelopmental condition. It is thought to have developmental roots in early in childhood and perhaps even in infancy (Auerbach et al., 2004; Sullivan et al., 2015). Thus, the maturational processes of self regulation are of central importance. In early precursive form, preschooler problems with self-regulation and early school age problems with inattention and impulsivity (as well as hyperactivity), which typically co-occur with irritability, are a risk factor for development of persistent aggression, mood regulation, or depression (although, importantly, this is not the only route to depression). While the picture for girls is somewhat more complex, most boys with conduct disorder also previously had ADHD, and the combination of ADHD and conduct disorder is a primary route to drug addiction and alcoholism. Thus, shared neurobiological mechanisms are expected in ADHD, conduct disorder, and drug addiction. The Psychiatric Genetics Consortium pooled genome-wide data (from arrays that assess hundreds of thousands of common variants called single-nucleotide repeats or SNPs) with a sample of some 30,000 individuals from one of five psychiatric disorders, including ADHD. Risk genes were identified that tended to be common across disorders (Smoller et al., 2013), although there was some nonoverlap for ADHD with the other disorders. Among child disorders, many neuropsychological findings seen in ADHD are seen in other disorders also, though sometimes with variations that support partial distinctions among conditions (Seguin, Parent, Tremblay, & Zelazo, 2009).

As might be expected from these intersections, many proposals for the psychological and neurobiological mechanisms involved in ADHD have been offered in the contemporary period (Barkley, 1997; Berger & Posner, 2000; Casey, Tottenham, & Fossella, 2002; Castellanos & Tannock, 2002; Douglas, 1972, 1999; Newman & Wallace, 1993; Nigg, 2001; Nigg, Swanson, & Hinshaw, 1997; Nigg, 2006; Sagvolden, Johansen, Aase, & Russell, 2005; Satterfield & Dawson, 1971; Sergeant, Oosterlaan, & van der Meere, 1999; Zentall & Zentall, 1983). Many are similar to what could be hypothesized for other disorders of impulse control. This nonspecificity is not belabored herein but should be borne in mind while considering genetic and neural findings in relation to inattention and hyperactivity-impulsivity or in relation to ADHD.

Overall, then, it is important to recognize that psychopathological categories exist in relation to underlying dimensions of liability, and also that they exist to some degree on a developmental continuum. Figure 14.1 shows one empirical estimate of how ADHD fits in with common types of psychopathology. It shows that hyperactivity-impulsivity tends to correlate strongly with oppositional defiance and conduct problems. Note, however, that even though inattention is placed on the externalizing factor in the figure, it is equally correlated with depression/anxiety symptoms. Also note that this helpful study by Lahey et al. (2008) did not consider the correlation of ADHD with learning disorders, autism, motor delays, or other neurodevelopmental conditions.

Few studies have done so. One study to consider this question, however, found that ADHD clustered strongly with ODD but also with autistic symptoms, motor coordination, and reading problems and that sibling cross

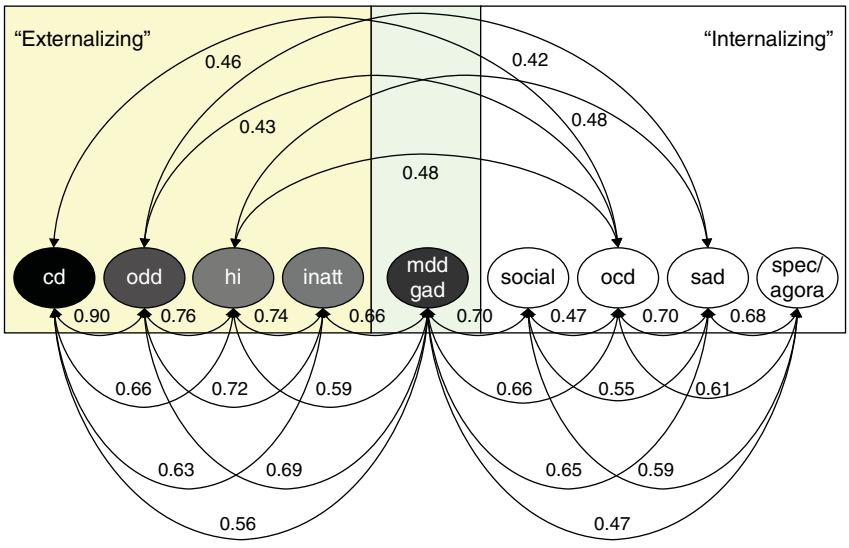


Figure 14.1 Correlations among child disorders. See footnote 1. *Source:* Reprinted with permission from Lahey, B. B., Rathouz, P. J., Van Hulle, C., Urbano, R. C., Krueger, R. F., Applegate, B., … Waldman, I. D. (2008). Testing structural models of *DSM-IV* symptoms of common forms of child and adolescent psychopathology. *Journal of Abnormal Child Psychology, 36*, page 196.

correlations loaded better for autistic, motor, and reading problems than behavior problems (Couto et al., 2009). Indeed, when one considers the overlap among symptoms of these disorders, it is striking that ADHD symptoms have a substantial phenotype overlap with motor delays (Fliers et al., 2009; Piek, Pitcher, & Hay, 1999; Pitcher, Piek, & Hay, 2003; Rasmussen & Gillberg, 2000); phenotypic overlap with autism spectrum disorders, (ASD) in that 50% of children with ASD are hyperactive and about 20% of children with ADHD have sufficient social oddity to raise questions about ASD overlap (Matson, Rieske, & Williams, 2013; Reiersen, Constantino, & Todd, 2008); have shared heritability with autism (Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010; Musser et al., 2014; Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010); and have cognitive problems including lower average IQ (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005) and learning disabilities (Willcutt et al., 2010), with which there is again genetic overlap (Couto, et al., 2009; Loo et al., 2004; Willcutt et al., 2002). Additionally, ADHD is associated with early appearing alterations in neural development (Castellanos et al., 2002; Shaw et al., 2007). These early brain alterations are not fully explained by differences in the structure of the genome (Castellanos et al., 2003) and so are due at least in part to either stochastic epigenetic changes or environmental influences on gene expression. While interesting neural signatures have been linked to callous-unemotional (psychopathic) traits (Breeden, Cardinate, Lozier, VanMeter, & Marsh, 2015), it is relatively difficult to demonstrate similar magnitude developmental brain changes in children with ODD or CD who do not also have ADHD. This is in part because such children are rare. A typical developmental progression is from ADHD (often accompanied by significant irritability early in life) to ADHD+ODD, and then to ADHD+CD; from there emanates one pathway to substance use disorders (Molina & Pelham, 2014). While many children with ADHD do not have ODD and many with ODD do not develop CD, most children with ODD also have ADHD, and nearly all children with conduct disorder, at least among boys, previously had ODD and ADHD.

The idea of a neurodevelopmental disorder is important for another reason: whereas ADHD is in part an extreme of a dimension of poor self-regulation, it is not only this. Substantial evidence indicates that ADHD also arises in relation to subtle neural injuries or developmental perturbations pre- and perinatally. These include prenatal teratogenic exposure, maternal severe emotional stress during pregnancy, low birth weight, or premature birth, particularly when other developmental conditions such as motor coordination problems or ASD symptoms, co-occur (Gillberg, 2003; Linnet et al., 2003; Nijmeijer et al., 2010; Owens & Hinshaw, 2013; Pearsall-Jones, Piek, Rigoli, Martin, & Levy, 2009; Sato, Aotani, Hattori, & Funato, 2004; Whitaker et al., 2011; Thapar et al., 2013). A caveat is that pre- and perinatal effects on outcome are difficult to detect after middle childhood (Wagner, Schmidt, Lemery-Chalfant, Leavitt, & Goldsmith, 2009) and are not necessarily causal. For example, maternal smoking in pregnancy seems to be largely a proxy for genetic risk, operating via gene-environment correlations (D'Onofrio et al., 2008; Obel et al., 2011; Thapar et al., 2009).

Even so, the weight of evidence indicates that in some instances ADHD is associated with poor self-control in the same way that a closed head injury is associated with poor self-control—that is, as a consequence of a subtle neural injury rather than as normal variation on a trait (Whitaker, et al., 2011). Thus, multiple etiological pathways must be borne in mind. In all, developmental paths to clinically significant inattention and impulse control problems are highly likely to involve both *equifinality*, meaning that several causal routes are contributory to ADHD, and *multifinality*, whereby early risks for ADHD may yield substantially divergent outcomes contingent on socialization and contextual processes (Cicchetti & Rogosch, 1996; Hinshaw, 1999).

Initial Comments on Etiological and Developmental Process

In the preschool years, the attainment of self-regulation, including arousal regulation, emotion, and attentional control, depends on socialization. It therefore is inherently an interpersonal process influenced by a complex interplay of child temperament (reactivity, presumably related to genetic and prenatal effects) and parent responsivity (Cecil, Barker, Jaffee, & Viding, 2012; Kim & Kochanska, 2012; Troxel, Trentacosta, Forbes, & Campbell, 2013; Ursache, Blair, Stifter, & Voegtline, 2013). In particular, family processes may be a primary mediator for the expression, over time, of the genetic mechanisms reflected in the substantial heritability estimates of these behavior problems, particularly in early life. School and community expectations for behavioral control also cannot be overlooked in considering the societal context of these problems.

Indeed, the contexts of children's development have changed rapidly in the past one hundred years in numerous ways beyond compulsory schooling. Diets have changed so much in the last century in the northern and western hemispheres that what most people in those societies

now eat has ceased to resemble the recent evolutionary diet, with complex effects on health that are still debated (Turner & Thompson, 2013; Walter & Ley, 2011). Hundreds of synthetic neurotoxins have flooded children's environments worldwide, including food, water, and air, with poorly understood consequences (Canfield, Gendle, & Cory-Slechta, 2004; Koger, Schettler, & Weiss, 2005; Lanphear, 2015; Nigg, 2006; Rice, 2000). In the last decade alone, the pace of technological change has been dramatic, continuing to change children's interpersonal and peer-relations throughout much of the world, through screen media exposure and social networking technology (Christakis et al., 2013; Sigman, 2012; Spies Shapiro & Margolin, 2013; Tandon, Zhou, Lozano, & Christakis, 2011). Political strife, upheaval, and violence have remained unfortunate realities for children in much of the world, often with substantial but poorly studied effects on the development of attention, self-control, and with them socialization, conscience, and interpersonal health (Betancourt et al., 2013; Betancourt et al., 2012). The meaning of ADHD in these varying contexts requires careful reflection, which this essay cannot fully address.

In the first world populations in which it has been primarily studied, ADHD (or its symptom domains) is highly heritable (Chang, Lichtenstein, Asherson, & Larsson, 2013; Kan et al., 2013). How do contextual and environmental pressures intersect with genetic effects? At times contextual forces are doubtless so powerful as to largely overpower genetic effects (e.g., an entire village of children forced to be child soldiers; Betancourt, et al., 2013). At other times, developmental contexts are sufficiently within the expectable limits for adequate development that genetic effects on individual variation are substantial. In short, when it comes to the complex behavioral picture of inattention and impulsivity, genetic effects are relevant, yet not directly causal or deterministic. Instead, two basic principles must be considered.

The first basic principal is that genetic and other child-specific mechanisms that influence individual differences in the expression of given traits or conditions (e.g., ADHD) do so within the context of effects on the entire population. For instance, individual differences in height are highly heritable, but the secular trends over the past century regarding substantially increased stature in the population at large (in developed and developing nations) are the result of environmental factors, such as more available calories. In the same way, population-wide changes in environment that influence level of a trait can contribute to children's attentional and regulatory problems regardless of heritability estimates within that population.

The second principle is that heritability estimates for nonmetabolic, multifactorial disease are better understood as heritability of liability than as heritability of disease. Put another way, genes likely influence susceptibility to psychiatric illness, while experiential events actualize that liability to varying degrees. This principle holds of liability even for infectious disease; heritability is substantial for tuberculosis, for instance (Fine, 1981) due to inheritance of vulnerability and protective qualities. Although specific considerations pertain to infectious disease, the same principle holds for behavior. This has been demonstrated in animal studies dramatically for some time. For example, Cairns and colleagues (Cairns, 1996) showed that in rodent populations bred to have nonoverlapping levels of stranger aggression, rearing in different socialization contexts fully eliminated this genetic effect in a single generation. This picture has helped drive strong interest in gene by environment (G×E) interactions, a theme later in this review.

Societal Context of Discussion: Medicalization, Controversies, Scientific Change

The clinical syndrome of ADHD and its treatment with medication has generated periodic and sustained controversy and social criticism for nearly half a century. This controversy requires comment to frame the current discussion. These societal discussions are provoked in part by ongoing secular increases in the numbers of children being identified with ADHD in the United States (Perou et al., 2013), although it should be noted that evidence of an actual increase in prevalence (as distinct from case identification), at least over the past two decades, is scant (Erskine et al., 2013). Western nations have also seen renewed concern about diversion of stimulant medication for nonprescription use for performance enhancement, leading to unintended health problems for users, which seizes media attention (Substance Abuse and Mental Health Services Administration, 2013; Tavernise, 2013). Clear data on the actual extent of such misuse, and whether it is related to rates of prescribing, is difficult to come by but nonetheless has become a significant concern in its own right (Kaye & Darke, 2012; Wilens et al., 2008; Weyandt et al., 2014).

Sociologists point out that *medicalization* occurs when a problem falls under the purview of the medical profession. For example, American society has seen the medicalization of pregnancy and birth, drinking problems, and other processes and conditions (Barsky & Borus, 1995; Conrad, 1992). The medicalization of attentional problems and hyperactivity, as well as disruptive behavior more generally, has long spurred critics to ask whether ADHD is a

valid psychiatric disorder (Searight & McLaren, 1998). It has also long sparked concern that rising medication rates may indicate an important shortage of other needed psychological or educational interventions for children (Safer & Krager, 1992) or that social control is being served rather than mental health (Menzies, 1997). The extreme forms of such criticism sometimes expressed are difficult to reconcile with the wealth of biological correlates of ADHD, from reliably reduced brain size (Castellanos, et al., 2002) from age 4 on, slower maturation of the cortical mantle (Shaw, Greenstein, et al., 2006), elevated levels of lead in their blood (Nigg, Nikolas, Knottnerus, Cavanagh, & Friderici, 2010), more family members with ADHD (Stawicki, Nigg, & von Eye, 2006), and differences in genotype (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010).

The issue to which critics may be trying to allude is that biological markers are not sufficient for clinical diagnosis in ADHD or, indeed, in psychiatry generally. Diagnosis relies on clinical judgment about behavioral symptoms. That judgment is only as good as the skill of the clinician and the quality of the evidence base upon which she relies. The ontological status of ADHD as a real condition with a definable biological process or marker that can be measured in all or nearly all cases of the disease (like it presumably can in cancer or infectious disease) is still some distance off and may never occur. It is likely that if such diagnostic biomarkers are ever identified, they will not apply to all individuals currently diagnosed with ADHD.

Indeed, for all complex diseases (hypertension, obesity, diabetes, cancer, and psychiatric conditions) the ability to identify a single biological cause is likely to be possible only when we can differentiate subgroups (as in breast cancer recently, for example). Complex disease is inherently characterized by probabilistic prediction based on risk factors that predict morbidity and mortality. ADHD conveys considerable morbidity risk (Nigg, 2013a), and thus examination of probabilistic diagnostic categories remains useful and important.

Whether these biological arguments will take a new turn remains difficult to say. It is striking that the past decade has seen a sea change in available scientific tools: the field now has access to affordable and powerful genetic assays, new tools for integrated systems biology, more refined imaging measures that assay the entire brain and its organization instead of just regions of interest, internet based large scale data collection, and ever more powerful computers that all enable the era of big data to come to bear on the study of human development and behavior. Most of these tools are only beginning to influence our understanding of ADHD, but it can be anticipated that they will do so to an increasing, if incremental, extent. With these considerations in mind, the discussion now turns directly to the syndrome of ADHD.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: BACKGROUND

The changes in conceptual definition of and treatment rates for ADHD over the years are one contributor to controversy about its status and meaning. It therefore is helpful to briefly review key historical aspects. More detailed historical background is provided by Nigg, Hinshaw & Huang Pollock (2006), Taylor (2011) and Nigg and Barkley (Nigg & Barkley, 2014), from whom I borrow liberally to set a contemporary context.

History

Well before current conceptual models began to be developed, educators and clinicians began to notice clinical-level manifestations of inattention, impulsivity, and dysregulated behavior in school-age children. Description of disorders of attention first appeared in the medical literature a little over two hundred years ago. As noted by Barkley and Peters (2012), Weikart (in 1770 or 1775) described adults and children who were inattentive, distractible, impersistent, overactive and impulsive, reminiscent of today's description of ADHD. As detailed by Taylor (2011), Crichton (1798) described patients with extreme mental restlessness.

The first American record comes from the physician Benjamin Rush, often credited as the founder of American psychiatry, who in his pioneering textbook in 1812 mentioned a syndrome involving inability to focus attention (Rush, 1812). Other references occurred in Europe periodically during that century. Interest picked up considerably, however, in first part of the 20th century, perhaps in relation to the implementation of compulsory education in the 19th century. By 1908, the term minimal brain damage had entered the medical lexicon (Taylor, 2011) to represent a group of children displaying substantial ADHD-like behavioral disturbances yet without evidence of gross brain damage.

Following the worldwide influenza epidemic during and after World War I, some children developed encephalitis, and it was noted that many survivors of this infection developed significant problems in attentional deployment, regulation of impulses, and general behavioral control, leading to the term minimal brain damage syndrome, a

term later softened to minimal brain dysfunction, or MBD (e.g., Strauss, 1947). By the 1960s, the boundaries of MBD had become far too over inclusive (Clements & Peters, 1962; Wender, 1971), and the term began to fall into disfavor.

Others were calling for narrower and more descriptive appellations. Laufer and Denhoff (Laufer & Denhoff, 1957) described a hyperkinetic disorder of childhood, focusing more specifically on dysregulated motor behavior. The second edition of the *DSM* (APA, 1968) adopted this narrower conception and nomenclature.

An empirical tradition was also expanding, in which parent and teacher ratings of child problems were subjected to factor analyses in an attempt to discern identifiable, empirically supported syndromes of psychopathology (Quay, 1972; Achenbach, 1966; Achenbach & Edelbrock, 1978). Factors labeled hyperactivity and immaturity emerged in such dimensionalized accounts of child problem behavior. Indeed, prior to *DSM-III* (APA 1980), ADHD was identified by extreme scores on these newly emerging ratings scales such as the Conners Teacher rating scale (Achenbach & Edelbrock, 1978; Conners, 1969; Pelham, Fabiano, & Massetti, 2005).

Based largely on the research of Douglas and colleagues (Douglas, 1972), in the 1970s and 1980s researchers in North America began to conceptualize the core deficit of children considered hyperkinetic as related to dysregulated attention and impulse control rather than motor overactivity per se. By *DSM-III* (APA, 1980), in the United States the condition had been renamed attention deficit disorder, which was posited to consist of a subtype with hyperactivity and a second, albeit undefined, subtype without hyperactivity. Meanwhile, in Europe the World Health Organization *ICD-9* (*World Health Organization, 1978*) continued to refer to hyperkinesis and to use a more restrictive definition that excluded many children with comorbid conditions who were still included in the *DSM* definition.

The empirical tradition continued, with efforts to develop empirically based taxonomies of children that included dimensions related to hyperactivity and inattention (Achenbach & Edelbrock, 1983). By this time, stimulant medication treatments, which had originated decades earlier with the pioneering work of Bradley (1937), were generating controversy (Sroufe & Stewart, 1973), a theme that continued (Jacobvitz, Sroufe, Stewart, & Leffert, 1990; Safer & Krager, 1992) and persists, as noted earlier.

Renamed attention-deficit/hyperactivity disorder for *DSM-III-R, DSM-IV,* and *DSM-5* (American Psychiatric Association, 1987, 1994, 2013), the condition's core subtypes were expanded in *DSM-IV* to three: a Predominantly Inattentive type (similar to the *DSM-III* notion of attention deficit disorder without hyperactivity), a predominantly hyperactive-impulsive type (unprecedented in previous nomenclatures), and a Combined type in which both symptom clusters were clinically salient. In *DSM-5* (APA, 2013), the structure of ADHD was largely unchanged although the subtypes were downgraded to presentations with text explaining their temporal instability.

Legislative changes in the early 1990s yielded the inclusion of ADHD as a potential trigger for special education services in public schools, while pharmaceutical companies began direct-to-consumer advertising, all increasing the salience of ADHD to families and clinicians. Prescription rates for stimulants, as for other psychotropic medications used with youth, doubled in the United States in the 1980s, repeated that in the 1990s (Safer & Krager, 1992; Safer & Zito, 1999; Zito et al., 2003), and continue to climb. Meanwhile, major clinical trials evidenced the efficacy of stimulant pharmacologic treatment for ADHD, if implemented carefully and with thorough monitoring, with combined medication-behavioral treatments yielding the highest likelihood of clinically meaningful improvement (Conners et al., 2001; MTA Cooperative Group, 1999). However, subsequent long term follow up studies indicate that the long term outcomes of brief intensive treatment were little altered (Molina et al., 2009), leading to an increased sense of the need to more fully understand pathophysiology and etiology.

Prospective longitudinal investigations were showing that ADHD was a condition likely to persist into adolescence in a majority of cases and to continue to yield impairment into adulthood in a substantial percentage (Mannuzza & Klein, 2000). Those findings led to the blossoming of research on ADHD in adults and the gradual recognition of the unique issues in establishing validity of the construct in adults, reflecting recognition of a research and clinical domain in ADHD that had been underway for a generation (Wood, Reimherr, Wender, & Johnson, 1976).

Thus, ADHD has for some time now been recognized as a condition that is not restricted to childhood or even adolescence. Yet the ongoing recognition of ADHD in adolescents and adults has in some ways exacerbated questions about the boundaries of normality when it comes to inattention and disorganization, as a harried, over-scheduled workforce and a student population driven by increasing competitive performance demands seeks relief and help.

In general, ADHD is currently understood as a clinically useful, statistically informative but not biologically meaningful cut point on a continuous dimension of behavior in the population (Larsson, Anckarsater, Rastam, Chang, & Lichtenstein, 2012; Levy, Hay, McStephen,

Wood, & Waldman, 1997; Levy, McStephen, & Hay, 2001; Willcutt, Pennington, & DeFries, 2000). It is provocative to consider whether this dimension we call ADHD in fact contains meaningful subconfigurations, which hew better to biological domains and that might isolate biologically more meaningful populations. That question is taken up in this chapter's concluding sections.

Clinical Features and Issues for ADHD

DSM-5 (APA, 2013) requires six of nine possible symptoms of inattention-disorganization or 6/9 symptoms of hyperactivity-impulsivity to be present for at least 6 months and to have onset prior to age 12 years. They must cause substantial interference in functioning and substantial features have to be present in more than one setting (e.g., home and school). The World Health Organization's *ICD-10 (World Health Organization, 1992)* is expected to be updated with an 11th edition in 2017 or 2018, shortly after this volume is published, but likely will not have identical criteria to *DSM-5*, reflecting ongoing differences in how this syndrome is viewed in Europe and the United States. However, because most research on ADHD uses a *DSM* or else a dimensional perspective, the present chapter refers to ADHD without differentiating potential distinctions with hyperkinetic disorder in the *ICD*. The prevalence of ADHD worldwide is estimated by recent meta-analyses to be between 2.5% (Erskine, et al., 2013) using fairly conservative criteria, to about 5% using slightly broader criteria (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Willcutt, 2012), with a male preponderance on the order of 2.5:1 in community samples. A handful of key issues with the clinical construct are important to note.

The diagnosis of ADHD requires not only above-threshold numbers of symptoms but also (1) the early onset of these symptoms, (2) their developmental extremity (a key point, given that problems of inattention and impulsivity are ubiquitous in young children), (3) their cross-situational display (i.e., at home, at school, and often in the peer group or work setting), and (4) the requirement that they yield functional impairment. These guidelines have strong empirical support. Thus, assessment requires, at a minimum, the taking of a careful history; reports from multiple adult informants with well-normed rating instruments; differential diagnostic procedures to distinguish ADHD from either normal developmental variation or a host of medical and psychiatric conditions that feature inattention and impulse control problems in their presentation; and, when possible, direct observation of the child in family and school contexts. Considering functional adjustment in multiple domains can assist with treatment tailoring (Pelham et al., 2005).

Willcutt et al. (2012) provided a thorough review of the empirical data regarding symptom dimensions and clinical subtypes, which yielded several important conclusions. First, a two-factor structure underlying the constituent symptomatology, corresponding to inattentive-disorganized and hyperactive-impulsive symptom domains, is valid and useful psychometrically. Both areas can be reliably measured by parent and teacher rating scale instruments. They show divergent validity, with inattentive behaviors uniquely associated with academic problems and hyperactive/impulsive behaviors aggregating with disruptive tendencies in school and home settings. (Factor analyses actually show that a three factor model, separating impulsivity from hyperactivity, fits slightly better but because the fit is excellent for two factors, this more parsimonious solution is preferred for most uses). Thus, the underlying dimensions of ADHD show considerable psychometric viability.

Second, however, the *DSM-IV* subtypes (nearly identical to the *DSM-5* presentation) had significant validity problems. For this reason, they were downgraded to presentations in *DSM-5*. These problems included lack of longitudinal stability (one type easily becomes another over time), lack of differential treatment response; and lack of differential clinical or cognitive correlates beyond those that are already attributable to the distinction between the inattentive and hyperactive symptom domains. However, almost no data have examined genetic or neuroimaging findings on putative subtypes or dimensions differentially. Family studies asking whether ADHD subtypes breed true have been mixed; one meta-analysis found a small but statistically significant familial separation of the combined and inattentive types (Stawicki, et al., 2006). Meantime, behavioral genetic analyses suggest that the HI type, unlike the others, is not heritable (Willcutt, et al., 2000); its validity in school-age children is doubtful (Willcutt, et al., 2012).

ADHD is heterogeneous and some form of subtyping is likely to eventually be useful, but this will probably entail revision if not overhaul of the existing presentations. In part, there remains considerable concern in the field about how to describe a group of children who appear inattentive and underactive, sometimes referred to as children with sluggish cognitive tempo (Barkley, 2013; Moruzzi, Rijsdijk, & Battaglia, 2013). Many of these children are likely included in the ADHD inattentive presentation, but some experts suspect they have a distinct syndrome unlike other children in that presentation grouping. A better subtyping

scheme would reflect neurobiological variation better, and might also yield superior clinical stability and prediction.

The *DSM-5* criteria provide some parenthetical examples pertaining to adults, but probably are still inadequate to capture the syndrome in adulthood. The hyperactive-impulsive symptom cluster is likely to be particularly salient during the preschool and grade school years but fades in frequency and intensity by adolescence. On the other hand, the inattentive-disorganized symptom cluster, which becomes most recognizable with the advent of formal schooling, is more stable throughout adolescence (Hart, Lahey, Loeber, Applegate, & Frick, 1995) and may present as serious problems with self-organization and executive functioning in adulthood that are not fully captured in the current symptom list. Further, the range of impulsivity in adults is likely far more complex than captured in the three impulsivity items in *DSM-5*, as is noted in my discussion of impulsivity later. An established literature suggests empirical bases for refining the conception in adults (Achenbach, 1991; Conners, Erhardt, & Sparrow, 1999; Kessler et al., 2010), but this literature has not yet reached sufficient critical mass to overcome the advantages to the diagnostic nomenclature of retaining similar symptoms across age for ADHD.

New impairments unique to adolescents and adults must be considered including risky sex, drug experimentation, driving accidents, problems with employment, and marital conflict (Barkley, Fischer, Smallish, & Fletcher, 2004; Nigg, 2013a). A final complexity unique to the condition in adults concerns the potential for misdiagnosis in relation to Axis II psychopathology, or, in other words, the possibility that ADHD may develop into an enduring maladaptive personality style or trait by adulthood (Kernberg & Yeomans, 2013).

ETIOLOGIES

Genetics

Family studies established long ago that ADHD breeds true, with a twofold to fourfold increased risk among first-degree relatives see (Stawicki et al., 2006). How much of this familial similarity is due to genes versus common family experiences? Numerous twin and a few adoption studies from North America, Western Europe, and Oceania have established that at least in those cultures, and primarily relying on parent ratings, substantial portions of liability are carried by genetic variation, with a heritability coefficient, averaged across many studies, exceeding .8 (Boomsma, Cacioppo, Muthen, Asparouhov, & Clark, 2007; Chang, et al., 2013; Grant et al., 2007; Kan, et al., 2013). Heritability estimates are lower, however, when teacher ratings and self-ratings are examined (Merwood et al., 2013), due to the fact that each twin has a different informant (Kan, van Beijsterveldt, Bartels, & Boomsma, 2014). Yet the heritability of a latent variable for shared parent and teacher agreement was .78 in one study (Derks, Hudziak, Van Beijsterveldt, Dolan, & Boomsma, 2006). Relatively few studies have examined twin concordance of ADHD diagnoses derived from full clinical evaluation or the combining of parent and teacher input on symptoms and impairment.

The variation in results for teacher vs. parent ratings raises questions of rater bias (known as contrast effects) as an influence on heritability estimates. Contrast bias (parents emphasizing differences more in DZ than MZ twins) inflates heritability estimates of activity level in preschoolers (Basque, Martel, Leduc, & Cantin, 2008). Such effects in ADHD ratings appear to depend on what rating scale is used. Reitveld et al. (2011) reported on a longitudinal study of a large sample of twins in Europe, with maternal CBCL ratings at four age points (3, 7, 10, and 12 years). Even with rater contrast effects controlled, heritability was above .7 at each age. Simonoff et al. (2011) confirmed maternal contrast effects but also noted biases in teacher ratings due to twin confusion (known as correlated errors), especially for MZ twins. In other words, many twins have the same teacher, and teachers have more difficulty keeping MZ twins straight in their minds. When these effects were accounted for, heritability was between .6 and .7 in developed nations. Inattention-disorganization and hyperactivity-impulsivity have partially distinct genetic influences (Nikolas & Burt, 2010), underscoring the importance of considering this two-domain structure in any statements about ADHD's etiology.

Nonshared environmental effects account for the remainder of variance in ADHD liability, which distinguishes it from conduct disorder (Burt, 2010). Thus, conduct disorder seems to have a greater component of shared environment than ADHD. This is consistent with a developmental model in which ADHD, a condition influenced by early genetic and nonshared environmental effects, gives rise via family and peer socialization processes to conduct disorder (Snyder, Schrepferman, Bullard, McEachern, & Patterson, 2012).

In response to these findings of high heritability for ADHD, researchers aggressively pursued molecular genetic studies during the period from the late 1990s to now. Some reflections on approaches to molecular genetic studies are in order to aid readers in evaluating his body of work.

In taking a molecular approach, one must consider the conceptual genetic model of the trait or disorder being studied. While this was largely guesswork in the case of psychopathology a decade ago, Figure 14.2 (Hindorff, Gillanders, & Manolio, 2011; Manolio et al., 2009) illustrates one general analysis that is influential in psychiatric and medical genetics of complex disease today. It shows that the magnitude of genetic effect on disease for individual genes grows smaller in a near logarithmic function as one proceeds from rare genes causing genetically simple diseases to common genes acting in concert to influence complex disease.

In the case of ADHD, the most common approach to studying molecular correlates in the past two decades was, from the viewpoint of this model, rather limited. The idea was to look for large effects in candidate genes using common gene variants. These were candidate genes because they were believed for theoretical reasons to be of interest, such as dopamine receptor genes. One early meta-analysis of that literature concluded that six genes have common markers that had been statistically associated with ADHD to date: dopamine transporter (DAT1), dopamine D4 and D5 receptors (DRD4, DRD5), serotonin transporter (5HTTPLR), HTR1B, and SNAP25 (Gizer et al., 2008). However, these in combination account for only 1% of phenotypic variance in ADHD and thus are not clinically useful, and their effects, in terms of our Figure 14.2, are small, with odds ratios around 1.1 (i.e., far too small to be of clinical interest, but potentially adding clues to pathophysiology overall, in conjunction with one another).

A second approach also assumes that ADHD is a product of common variants (the common disease + common variant model), but takes an agnostic approach to which genes are involved. The approach therefore scans the entire genome, called a genome-wide association (or linkage) study or GWAS. With this approach searches are conducted across hundreds of thousands of common markers (usually a particular type of marker called single nucleotide repeat or SNP) distributed across the genome. Somewhat to the surprise and disappointment of many scientists, genome-wide scans generally failed to identify important new genes in ADHD. However, when we consider Figure 14.2, in retrospect this result is not especially surprising. The model in Figure 14.2 predicts that the effects of individual variants are quite small. In GWAS, thousands of statistical tests are required, resulting in low statistical power to detect these small effects. Indeed, individual markers have not been seen reliably for most complex diseases or traits until sample sizes have reached into the range from 10,000 to 30,000 samples. Yet most studies of ADHD used only a few hundred to a few thousand samples.

Nonetheless, a few interesting findings emerged from GWAS of ADHD so far. Novel candidates may warrant follow up, including one that is under a genome-wide significant linkage peak in a meta-analysis, cadherin 13 (CDH13) (Lasky-Su et al., 2008). This gene is expressed in nicotinic receptors and involved in neurite outgrowth (Canino & Alegria, 2008). Further, specific genetic effects, particularly related to central nervous system development, are shared across several major psychiatric disorders (PGC,

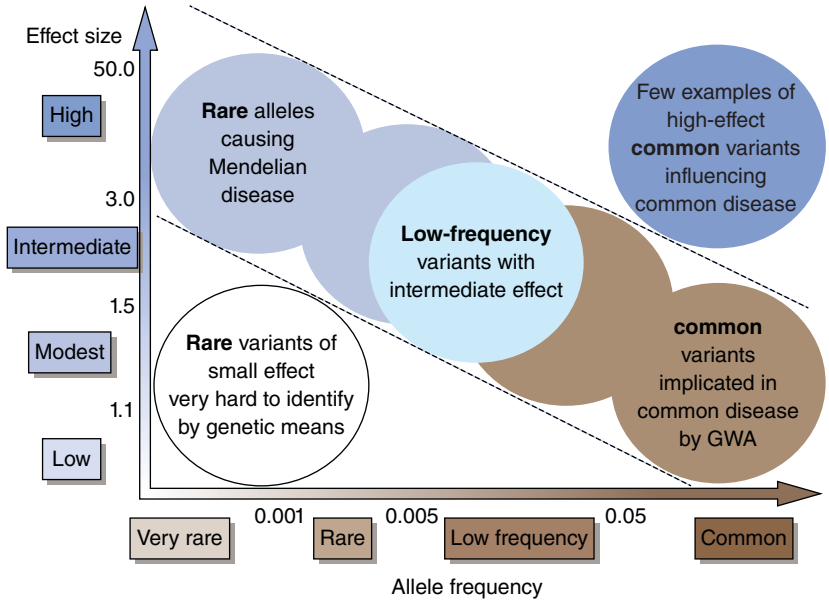


Figure 14.2 Molecular genetic meta-model. See footnote 1. *Source:* Reprinted with permission from T. A. Manolio, F. S. Collins, N. J. Cox, D. B. Goldstein, L. A. Hindorff, D. J. Hunter, . . . P. M. Visscher (2009) Finding the missing heritability of complex diseases, *Nature, 461*(7265), page 749.

2013; Lotan et al., 2014) although ADHD does not fully share in this overlap (Smoller, et al., 2013).

Perhaps most interesting at the present juncture are analytic methods that manage to sum up the effects of all the variants on a chip, whether or not they are initially significant (for description of these methods, see Wray et al., 2014). This approach reveals that when all the common variants are taken into account, in aggregate they account for about 25% of the genetic variance in ADHD (PGC, 2013). Insights regarding molecular genetic overlap of ADHD with other traits and disorders are accordingly now possible and beginning to emerge at a rapid pace as of this writing (Hamshere et al., 2013; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2015).

These polygenetic analyses confirm that common variants are important, but underscore that they do not act primarily via single gene effects but rather act in concert. That is, they likely operate in ADHD via their joint involvement in biological and metabolic systems. Those systems must now be described (next paragraph). Second, as corollary, other kinds of gene effects not due to common variants are carrying much, perhaps the majority, of the genetic variation in ADHD.

To build on the first of these hard-earned realizations, about the aggregate activity of common variants, will require organizing common gene variants into their chemical and physiological groupings, called gene-based pathways. This approach tests for significant association with an over- or underexpressed pathway and thus has more power than searches for individual markers. A small number of handful studies have attempted this approach with ADHD. Results, while preliminary, are intriguing, linking ADHD to gene pathways involved in synaptic transmission, nicotinic receptors (already one of the biochemical theories of ADHD), neuritic growth, and CNS development (Bralten et al., 2013; Cristino et al., 2014; Hammerschlag et al., 2014; Poelmans, Pauls, Buitelaar, & Franke, 2011; Stergiakouli et al., 2012; Yang et al., 2013). Whether these specific findings will reproduce remains to be seen, but it is likely that more gene-pathway-based approaches will be fruitful in the near future and will eventually converge on new insights.

To build on the related insight, about effects of noncommon variants, requires still another approach. Here, a different model is assumed. As also illustrated in Figure 14.2, instead of a common disease + common variant model, one now adopts a common disease + rare variant model. Here the assumption is that numerous distinct, but individually rare, genetic events are all giving rise to the same syndrome. The goal is to discover some of these rare structural variants, in hopes of gleaning new insights into pathophysiology that may apply to the syndrome more broadly.

Many of these are rare copy number variants (meaning the only difference in the allele is that a given nucleotide sequence is repeated too many times). They can be found by re-analyzing GWAS data. These studies are beginning to emerge on a regular basis and implicate genes involved in neural development, suggesting the beginnings of genetic clues to pathophysiology. Studies of this type are emerging at a steady pace (Elia et al., 2010, 2011; Jacob et al., 2013; Jarick et al., 2014; Lionel et al., 2011; Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014; Williams et al., 2010). It has been hypothesized that 10–15% of the genetic variation in ADHD may be due to these CNVs. To date, work has been limited because only fairly large variants could be seen to date. As the ability to see smaller perturbations in the genome emerges, more findings in this area will emerge.

Still other rare variants can be discovered by looking within family pedigrees and sequencing exomal regions of the genome (nonsynonymous variants) or by sequencing the entire genome. Both methodologies are on the cusp of widespread application. Novel rare variants are expected, and likely to be discovered, in the process, but each will pertain only to a small fraction of the population with ADHD. If enough are discovered that have large effects, clinicians can test for them, but the real payoff may be in determining their pathophysiological activity to discover more about how ADHD develops in the brain more generally.

Last but far from least, the unexplained genetic variation in attention deficits, impulsivity, and dysregulation may be due to gene × environment interaction or epigenetic effects. This idea is of central importance and the implications are substantial from a multilevel, developmental psychopathology perspective.

Gene–Environment Effects

In the past decade, studies of gene–environment (G×E) effects have become standard in research on development, developmental psychopathology, and clinical disorders. Ever more sophisticated process models are now available, and G×E is approaching the level of a new paradigm for behavioral studies generally, with entire special issues of major clinical and scientific psychopathology journals devoted to G×E in the last couple of years (Nigg, 2013a, 2013b).

The still emerging literature on GxE effects on inattention, impulsivity, activity, or ADHD is promising. An early review (Nigg, Nikolas, & Burt, 2010) indicated reliable and consistent interactions of psychosocial distress measures and genotype for particular candidate genes, notably serotonin transporter and dopamine transporter. Subsequent

work continues to generally support this picture using a range of measures of psychosocial stress and expanding to other candidate genes (Berry, Deater-Deckard, McCartney, Wang, & Petrill, 2013; Elmore, Nigg, Friderici, Jernigan, & Nikolas, 2015; Li & Lee, 2012, 2013; Riva, Marino, Giorda, Molteni, & Nobile, 2015; Sanchez-Mora et al., 2015; van der Meer et al., 2014; van der Meer et al., 2015). However, these studies have generally relied on one or two candidate genetic markers in relation to selected measures of the environment. The hazards of such studies are many. In particular, (1) the environmental measures may be influenced by unmeasured genes and (2) if the allele frequencies are sub-optimal or environmental measures not properly scaled, statistical artifact can easily result (Eaves et al., 2000). Nonetheless, the general picture is that GxE effects are gaining considerable support as a key mechanism in ADHD etiology.

While better modeling will be needed to identify particular genes and particular environments and how they interact, the general approach already shows that larger genetic effects can be seen when looking within different environments. Now, with the existence of G×E established in specific instances and widely accepted conceptually, a particularly salient question for the G×E effect in the development of ADHD as well as normative self-control and self-regulation concerns the nature of the interplay. The idea that different forms of interaction exist and can be distinguished was first proposed over two decades ago by Aiken and West (1991), and has now been rediscovered in the area of G×E for a range of child characteristics (Belsky, Pluess, & Widaman, 2013; Pluess & Belsky, 2011). Figure 14.3, adapted from a recent paper in this genre, illustrates the central question.

The top panel of Figure 14.3 schematizes a vulnerability model. In some environments, genetic risk is not activated, but in other environments it is. This model, consistent with a classic diathesis stress model, has long been the best, if underutilized, general model in psychopathology. The bottom panel illustrates an alternative, which is called a susceptibility or plasticity effect. Here, the clinical genotype is actually a genotype that is maximally responsive to the environment. The genotype confers not vulnerability but *responsivity*. Under negative environments, one sees the typical poor outcome for the risk genotype. But in advantageous environments, the same genotype can have a superior outcome to the alternative genotype.

Numerous hazards accrue to attempting to statistically distinguish these effects. To name just one obvious one, the top panel, extended to infinity, would presumably

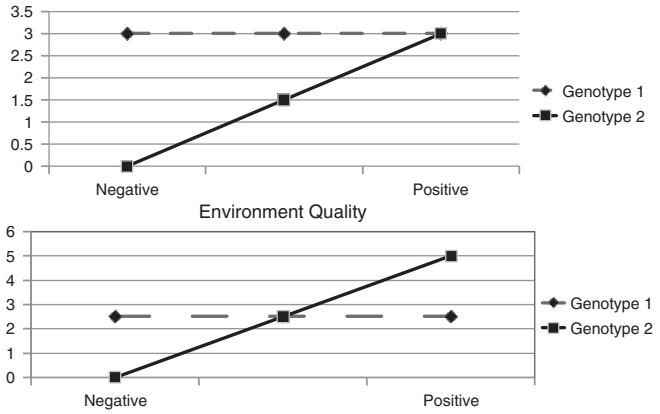


Figure 14.3 Vulnerability versus susceptibility models of G×E effect. *Source:* Adapted with permission from J. Belsky, M. Pluess, & K. F. Widaman, (2013) Confirmatory and competitive evaluation of alternative gene–environment interaction hypotheses, *Journal of Child Psychology and Psychiatry, 25*, page 1136.

eventually show the cross over pattern. However, at a practical level, this and other problems may be addressed with appropriate scaling, consideration of range, and other methods. Now, empirical studies have begun to distinguish plasticity from vulnerability effects in the area of parenting, temperament, and outcomes related in self-regulation of attention and impulse in early childhood (Kochanska & Kim, 2013b; Kochanska, Kim, Barry, & Philibert, 2011).

Further, recent years have seen exciting developments in epigenetics, that is, the recognition that experience can alter the genome—and thus the phenotype—sometimes dramatically. This represents at least one mechanism by which G×E can occur. Epigenetic modification occurs in several ways; one well-known way is through DNA methylation, which entails modification of chromatin, the material in which DNA is housed, to alter gene expression. That is, the expression of much of human variation may not depend only on DNA structure but on the regulatory markings that control whether and how a gene is expressed. Because these mechanisms remain speculative for ADHD, attention, and impulsivity, I do not elaborate further here. However, epigenetic mechanisms may prove extremely important in understanding human behavioral and cognitive development so I return to them later when considering future directions.

These two insights (the importance of G×E and the importance of epigenetic effects) have sparked a renaissance in studies of environmental contributions to ADHD (as well as several other psychiatric conditions) that is changing the face of research in the second decade of

the twenty-first century and may potentially also change the face of clinical practice in the decades that follow. Therefore, the role of the environment in the development of self-regulation, self-control, and ADHD is likely to be much more important than was widely believed ten or twenty years ago. However, this will be a modified understanding from even earlier days when ADHD was assumed to be entirely environmental. Instead of looking at environmental main effects, the field will undertake more specification of for whom (genetically) environments are exerting their effects on development and how (by modifying gene expression) they are doing it.

When it comes to the environmental effects, they must be considered at multiple levels of analysis and stages of development. We can consider the prenatal environment, where maternal diet and maternal stress likely exert influences on the developing fetus. We also can consider the early socialization environment. One interesting gap in our knowledge concerns very early socialization influences on later ADHD. The belief has been that disrupted parenting and discordant parent–child interactions result from, rather than cause, temperamentally mediated child noncompliance and impulsivity. This assumption is well supported by existing data, although problematic parent–child relationships may well be significant maintaining and exacerbating factors related to ADHD, yielding reciprocal, transactional chains of influence in conjunction with the child's core symptomatology (Hinshaw, 1999; Johnston & Mash, 2001). However, nearly all of the studies that support that view were conducted with children beyond the toddler years. Essentially nothing is known about the role of parent–child interchanges in the first year or two of life in ADHD.

ATTENTION AND IMPULSE CONTROL IN DEVELOPMENT: DUAL-PROCESS PERSPECTIVE

In thinking about how attention and impulse control develop, a heuristic model is helpful to organize the vast array of ideas and information available. Here one can gain considerable insight from a fundamental and ubiquitous approach in psychology, known as a hierarchical two-process model. Later it will be noted that more than two processes are involved ADHD. Nonetheless, while this is not a formal model, it provides substantial help with conceptualizing and organizing work in this field.

TABLE 14.1 Type 1 and Type 2 Regulation and Commonly Used Terminology

Type 1	Type 2
Reactive	Effortful
Automatic	Deliberate
Fast	Slow
Incentive motivated	Goal motivated
Hot	Cool
Bottom-up	Top-down
Develop early	Develop late

Two-process models must include the following elements: (1) type 1 process, (2) type 2 process, and (3) resource capacity or motivation[2] that influence the decision set points for which process will engage—in this case, the set point at which Process 2 is invoked to override Process 1. Models of this general nature, with varying specifics, are found historically in the ADHD literature (Nigg, 2001; Nigg, 2000b; Sergeant, et al., 1999; Sonuga-Barke, 2005; Sonuga-Barke, Dalen, Daley, & Remington, 2002), in theories of personality and temperament that relate to self-regulation (Block & Block, 1980) and are in concert with cognitive and social psychology models dating back over 30 years, as several excellent reviews attest (Evans, 2008; Evans & Frankish, 2009; Evans & Stanovich, 2013; Kahneman, 2011).

The perspective herein builds on earlier work by the author and collaborators (Nigg & Casey, 2005; Nigg, 2001, 2000b, 2006), complemented by related work by others (e.g., Sonuga-Barke, 1998; 2002), introduces some modifications in light of recent work in cognition (Evans & Stanovich, 2013), and uses this to describe a heuristic model that can usefully guide thinking both on ADHD and on the overall idea of self-regulation of attention and impulse and its development. From this perspective, the developmental psychopathology story is organized as it relates to disturbances in self-regulation and to ADHD.

The model has two distinct processes; they can be thought of as two aspects of a single system or as two systems (while experts in fact debate this last nuance, for present purposes either view is acceptable). These are termed type 1 and type 2 processes and heuristically summarized by their common appellations in Table 14.1.

Type 1 processes provide automatic handling of routine information, emergency reaction, and alert us to salient and unexpected information. Type 1 processing is the pre-

[2]The capacity or motivation aspect is also part of the model if it is recast as a single-process models with two aspects (Kruglanaski, 2012).

sumed default: most behavior is automatic, presumably to conserve the organism's energy. Type 2 processes override stimulus-triggered responses and allow us to regulate our focus and our action in response. How does the mind determine whether to follow type 1 processing or to invoke the more costly and resource-intensive type 2 processing? This determination must take into account both the incentive value of the problem (motivation) and overall available resources (energy, arousal, and intellectual or working memory capacity). Therefore, the model must also include capacity or resource constraints that influence relative involvement of type 2 processes in a given situation.

Proposals for what goes wrong in ADHD invariably invoke a breakdown in type I, type 2, or resource-capacity domains (or combinations thereof) to explain the syndrome. A critical question for theory of ADHD is, therefore, this: does regulatory failure occur because the type 2 process, once invoked, was ineffective? If so, was this ineffectiveness due to insufficient capacity or resources or to some other problem? Or does failure occur because the type 1 process failed to function properly and did not invoke the type 2 process in the first place? Theories of ADHD can be grouped according to which of these scenarios they emphasize.

Type 1 Process

Type 1 regulation is characterized by relatively automatic or autonomous processing. It is stimulus driven, rapid, occurs without intent or volition, and requires minimal working memory resources or application of attentional control. As conceived in relation to attention and impulse control, it is implemented primarily in posterior and subcortical neural networks, although functionally connected frontal brain areas can also be involved. It can interrupt deliberate activity, or be suppressed by it, but it is distinguishable from deliberate mental activity. An example of type 1 regulation is when behavior is automatically interrupted in response to a surprising sound or a frightening event (an example of subcortical activation sending involuntary signals into the attentional sphere and interrupting working memory and motor programs; (Gray, 1982; Gray & McNaughton, 1996; Kagan, Reznick, & Snidman, 1987), or when attention is automatically captured by a sudden movement (an example of a ventral attention network sending signals to the cognitive control system). In each case, attention automatically reorients to the new event, and other behavioral routines are interrupted. Thus, when she notices something anxiety provoking, a child may direct her attention to the concerning event or person—reallocating and narrowing the focus of attention (Derryberry & Tucker, 1994).

An important principal in a dual-process account of self-regulation or ADHD entails the intersection of emotion and cognition (Nigg & Casey, 2005). In many psychology writings, type 1 processing is associated with relatively more affective response and type 2 with relatively less affective response and more cognitive processing or reasoning. While that summary has some value, readers are encouraged to think integratively about how emotion and cognition interplay in the moment-to-moment regulation of behavior. That is, emotion-free cognition and cognition-free emotion do not really occur. Rather, we are referring to the relative strength of emotional arousal.

Put another way, the incentives that shape attention can be sufficiently immediate as to triggering "hot" type 1 processing, or sufficiently distal as to require "cool" or type 2 strategic processing to attain them. Thus, even though attention is usually viewed as a cognitive process, it is just as often (if not always, to some degree) motivated by incentive concerns. These same incentives can also influence impulse control, leading either to a very strong impulse to action (e.g., excitement from an imminent reward) or to inhibiting some or all behavior (e.g., confrontation with an anxiety-provoking or unfamiliar situation). Such motivated responses are often relatively spontaneous, and they are relatively more automatic than the more deliberate responding characteristic of effortful control. In short, the type 1 response, often called the prepotent response in ADHD theories, can arise for multiple reasons—emotional salience (fear or excitement, which are associated heuristically with limbic circuits, in particular the amygdala), overlearning (associative or implicit learning, which can be associated in part with striatal structures), or response set (multiple prior instances of an overpracticed response). In each case, the response is activated without intent. It has become, or always been, automatized.

An interesting possibility, though largely bypassed here, is whether children with ADHD have difficulty automatizing behavior (Huang-Pollock & Karalunas, 2010). That is, in ADHD self-regulation may remain excessively dependent on type 2 process when it should not, hurting overall regulatory efficiency and causing effortful tasks to be overwhelming. An analogy would be poor readers for whom each word is effortfully sounded out rather than effortlessly recognized.

Type 2 Process

Type 2 regulation is characterized by demand on working memory or attentional resources, is experienced

subjectively as effortful or deliberate, is controlled, and is capacity limited. Its outcome is not automatic, but flexible (see thoughtful discussion by (Thompson, 2013). An example of such regulation is when I consciously bite my tongue to avoid interrupting a long-winded colleague so as to keep a New Years' resolution to be more patient. It is implemented to an important extent in prefrontal cortex, although it also involves the anterior cingulate cortex, and several other cortical and subcortical brain areas become involved due to their functional connection to prefrontal cortex. It serves to prime, bias, direct, or suppress the type 1 processes. This suppression is hypothesized to be implemented neurally by exertion of inhibitory projections backward to parietal cortex and downward, particularly via frontal-limbic-thalamic and frontal-striatal-thalamic and cortical-subcortical neural circuits.

Type 2 processing can be linked with productive concepts from the study of preschool temperament that refer to *effortful control*—the ability to delay or interrupt task-inappropriate behavior (Rothbart & Bates, 1998), or to assign positive motivation to a required task (Kochanska, et al., 2011). Effortful control shows longitudinal stability, with high scores for this ability associated with development of adaptive behaviors (Kochanska, Murray, & Coy, 1997; Kochanska, Murray, & Harlan, 2000), it also was helpful associations to developmental psychopathology, which help us integrate multiple literatures. Thus, excessively *high* control is associated with internalizing problems, while *low* control is associated with externalizing behavior problems over the preschool years (Murray & Kochanska, 2002).

Type 2 processing often requires working memory, and so is related with the idea of executive functioning, which has been a common neuropsychological approach to conceptualizing ADHD. It is widely agreed both that executive functioning is central to understanding attention and impulse control and that it is an underspecified construct (Pennington & Ozonoff, 1996; Zelazo et al., 2003). In a neuropsychological framework, executive function refers to strategic or relatively deliberate regulation of response to context and maintenance of behavior in relation to goals (Pennington & Ozonoff, 1996). While often supplanted by the more contemporary term cognitive control, the concept of executive function has additional connotations. It seems to reflect several component operations of which working memory is one; other important abilities include the capacity to temporally sequence information (Castellanos & Tannock, 2002; Fuster, 1997)—part of a broad but not a narrow conception of working memory (Baddeley, 2012), the ability to suppress prepotent responses whether or not information is being held in working memory, and the ability to shift set. Numerous proposals for how to componentialize executive functions testify to its historical under-specification as well as its substantial heuristic utility (Barkley, 1997; Dempster, 1993; Engle, 2002; Friedman & Miyake, 2004; Logan, Cowan, & Davis, 1984; Lyon & Krasnegor, 1996; Mirsky & Duncan, 2001; Miyake et al., 2000; Monsell & Driver, 1998; Nigg, 2000b; Pennington & Ozonoff, 1996). This reflection on executive function also underscores the close relationship of the neural bases of deliberate control of attention and impulse (as well as the regulation of emotion) (Nigg & Casey, 2005; Posner & Rothbart, 2000).

With regard to impulse control, similar frontal-subcortical neural circuits are implicated in suppressing responses (Casey, et al., 2002). For example, suppressing inappropriate motor response during complex behavior appears to involve the dorsolateral prefrontal cortex, at least in young children (Diamond, Prevor, Callender, & Druin, 1997), as well as the orbitoprefrontal cortex (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Posner & DiGirolamo, 1998) and the subcortical connections to each. Indeed, the subcortical and striatal structures to which these prefrontal regions are connected may be crucial in the actual suppression of a response (Kimberg & Farah, 1998) at least in certain contexts (Nigg & Casey, 2005). A developmentally oriented process conception of executive functioning emphasizes deliberate problem-solving steps, such as representing and manipulating the problem in working memory (planning), carrying out an intended action rather than a competing action, and detecting mismatch to expected results or success (Zelazo et al., 2003). Those functions likewise have clear relevance to attention and impulse control and all refer to type 2 regulatory processing.

Development, Socialization, and the Two-Process Model

The development of these neural and behavioral systems is in constant interplay with the child's interpersonal world as elaborated in more detail by us in the second edition of this handbook (Nigg, Hinshaw, & Huang-Pollock, 2006) via mechanisms like parenting attunement, verbalization of affect, and subsequent routinization, limit setting, and other activities, all of which operate in complex interchange with child reactivity and control to shape consolidation of self-regulation (Choe, Olson, & Sameroff, 2013; Kochanska & Kim, 2013a, 2013b; Koenig, Barry, & Kochanska, 2010). Neural development and self-regulation cannot develop apart from the early

parent–child relationship. Indeed for the first few months of life the mother provides the type 2 processing for the child and is the child's regulatory system in many respects. Scaffolding by caregivers in the early rearing environment, the modulation of stress, and the success of early learning all emerge as important in the early developmental consolidation of both type 1 but particularly type 2 self-regulation (Barry, Kochanska, & Philibert, 2008; Cecil et al., 2012; Kochanska & Kim, 2013b; Koenig, et al., 2010). Furthermore, it is likely that the aforementioned gene × environment interactions affect how parenting and child temperament interplay (Rothbart & Posner, 2005; Sheese, Rothbart, Voelker, & Posner, 2012). In short, while the current essay elaborates the within-child components of cognition and self-control, readers should be cognizant that interactions and transactions between within-child factors and environmental influences are crucial in any complete account of how self-regulation, inattention, or impulsivity develop. The transactional account is constrained in this chapter due to space, not due to its developmental importance.

Type 1 processes mature more rapidly than type 2 processes, commensurate with the brain's developmental maturation from rostral to caudal and the importance of prefrontal cortex in the implementation of advanced type 2 processing. Thus, behavior of young children is relatively less governed by type 2 processing than behavior of adults. Behavior of toddlers reflects relatively more precursive type 2 or effortful self-regulation than behavior of infants.

Infants allocate their attention (and their motor responses) simply on the basis of stimulus response and reflex response, which are largely midbrain-mediated processes that correspond to the reflexive attentional mechanisms discussed earlier. However, by later in infancy, sometime in the 1st year of life, children begin to respond to cues for incentives by directing their attention and making motor responses such as approaching a potential reward or withdrawing from a potentially distressing signal (Rothbart & Rueda, 2005). These latter responses correspond to affectively based type 1 allocation of attention and control of behavior. By the beginning of the toddler period, roughly about the age of 14 months, infants can be observed to deliberately turn their attention away from upsetting material, exemplifying a precursor to deliberate regulation of behavior and affect by executive control, and thus the beginnings of self-control (Rothbart & Bates, 1998).

In the toddler years, type 2 control of attention and impulse, in the guise of effortful control, develops rapidly. By about 30 months of age, children can begin to inhibit stimulus-driven motor response (Diamond et al., 1997; Rothbart & Posner, 2005). For example, by this age, they can engage in interference control, go/no go, and stopping tasks (Diamond et al., 1997). Diamond and colleagues documented a steady development in the ability to inhibit competing, stimulus-driven motor responses by ages 3, 4, and 5 years; similar work is reported by Zelazo and colleagues (2003).

In middle childhood, many aspects of type 1 regulation mature, while type 2 regulation continues to develop. Huang-Pollock, Carr, and Nigg (2002) compared children in second through sixth grades on a computerized selection task evaluating two kinds of attentional selection. Late selection was progressively more mature in the older groups. Even sixth-graders were still well below adult level capabilities, although they were notably better than fourth graders. In contrast, early perceptual selection was essentially fully mature, at adult levels, even in the second-graders (Huang-Pollock et al., 2002). Similarly, Reuda et al. (2004) examined exogenous orienting (type 1), alerting (arousal) and strategic orienting (type 2). The exogenous orienting was essentially fully developed by the 6–9-year-old age period. All of these data are consistent with the proposition that relatively automatic type 1 processes develop earlier and complete their development at a much younger age than do cognitively demanding type 2 processes.

This general pattern of development mirrors the nonlinear and dynamic development of the brain systems involved. In particular, the cortical mantel develops in a partial caudal-rostral gradient, but with a peripheral-to central tendency, so that the most anterior and posterior portions of the cortex mature first, followed by regions of prefrontal cortex. In addition, myelination as well as pruning of neural circuits to improve their specialization and efficiency proceed all the way into early adulthood (Benes, 2001).

In adolescence, the picture becomes more complex because cortical and subcortical brain regions and their supported capabilities are maturing in nonlinear, dynamic fashion. Thus, important changes in type 2 processes and regulation occur during adolescence. Here some aspects of controlled attention reach adult levels, but many aspects of impulse control do not. In particular, it is interesting that cool executive function or response control without strong emotional or incentive content improves in linear fashion and reaches adult levels by about 20 years of age (Hare et al., 2008). However, when hot decision making is involved (imminent emotional information and in particular, social cues of emotional salience), then adolescents have more failures than children or adults

(Casey & Caudle, 2013; Casey et al., 2011). Thus, adolescents have a unique impulsivity around socially heightened reward or reward-salient cues that will alter the risk profile for those with ADHD or with propensity to impulse control disorder. At the same time, in adolescence demands for cognitive control increase (e.g., multiple class schedules in high school) that require more executive functioning; those who are weak in this area may start to see more clinical impairment. Hyperactivity normatively levels off in adolescence (an ADHD adolescent does not run around the room, the way a 6 year old with ADHD does).

In turn, as the child matures in the social context, the strength of this two-process self-regulation system is likely to influence the child's capacities to be normally socialized by average expectable parenting and peer environments (Cicchetti & Lynch, 1995) and achieve adequate socialization adaptively in adverse or suboptimal caregiving environments. The import here is that if a child has very strong reactive processes (e.g., extremely strong negative affect), these may interfere with development of effortful control, in turn further weakening ability to regulate the reactive affects. Conversely, weak effortful control as an early temperamental characteristic could lead to difficulty with affect regulation as part of a two-way mutual influence process. This formulation may help to explain why executive and affective difficulties so often co-occur in children with disruptive behavior problems and ADHD.

Additional Considerations

Hierarchy Model of Complexity

This last point highlights that type 2 processes are not all unitary, but rather exist on a hierarchy of complexity. Representing a stimulus-response association is less abstract than remembering that the association only applies in certain contexts, that is, a meta rule. Likewise, considering an action's consequences in the next few minutes or hours is not the same operation, nor does it rely on the same neural bases, as considering consequences over much longer time periods. It can be argued that in the brain a rostral-caudal control gradient organizes type 2 or control processes, with the most anterior aspects of PFC involved in the most abstract (meta-rule, or time duration) control tasks and operations (Badre & D'Esposito, 2009). Because anterior PFC projects unidirectionally to premotor cortex, as well as bidirectionally with dorsal and ventral lateral prefrontal cortex as well as medial prefrontal cortex (Petrides & Pandya, 2007), it is anatomically reasonable to consider top-down control operations to be involved in both motor and attentional control. This becomes important later when considering recent advances in neuroimaging of ADHD.

Functional Linkage of Attention and Impulse Control

Both for expository purposes and functionally, the elements of attention and impulse control can be understood as partially distinct. They do not always operate in perfect tandem; they may develop at different rates and they can be measured in distinct ways. In particular, attention can regulate mental processes, even when no motor behavior occurs. While one can speak of cognitive impulsivity (e.g., racing thoughts in hypomania, or inability to suppress thoughts in ADHD), to avoid confusion, regulation of mental contents is treated here under the purview of attention. The term *impulsive* is reserved for overt motor responses and to decision making that results in an associated motor, vocal, or overt emotional response.

Yet this separation of attention and impulse control should not be overstated. Attention and impulse control are closely related both functionally and developmentally. This is important because it is tempting to link problems in regulation of impulse with faulty type 1 processing and problems in regulation of attention with faulty type 2 processing. While doing so can be helpful in some respects, it is a misleading simplification in terms of development or neural function. Attention can regulate impulse and impulse can capture attention. As noted earlier, for a young infant attention is captured involuntarily by an attractive object and she reaches for it automatically (type 1 process). Soon thereafter, a toddler can deliberately look away from a tempting but forbidden object, using attention to regulate impulse as well as emotional arousal (type 2 process). Thus, from early infancy on, attention assists with self-regulation and impulse control (including emotion regulation, behavioral control, and cognitive control) (Pollak & Tolley-Schell, 2004; Rothbart & Rueda, 2005).

Functionally, some kinds of individual variation in impulsivity can be seen as variation in stylistic features of type 2 processing, that is, simply preferences for reflective or nonreflective decision making. Other kinds of individual variation in impulsive decision making are not so easily seen as part of type 2 process, but rather as type 1 process (e.g., intensity of response to incentive). Further, in day-to-day behavior attention and impulse often act in concert or in tension. Both can be influenced, for example, by sensory reflex response. Likewise, both are influenced by strong affective arousal. In the case of strong anxiety (signal of *possible* threat) or fear (*actual* threat), attention is captured and existing impulses are suppressed and replaced by impulses related to the anxiety or fear

(e.g., impulse to flee). In the case of strong excitement due to potential reward, attention is captured and impulses are activated toward the incentive. Likewise, as noted before, the neural systems that support certain attentional skills are closely related to those that support control of motor responses, or impulses (Calkins & Fox, 2002). Further, one can easily think of intersections that do not easily map on to a discrete process model. If the keys are locked in the car because I got distracted as I quickly slammed the door, which impulse control process is faulty? Or is the impulsive action actually an instance of inattention?

Summary Comments About Two-Process Model

An essential qualification is that both attention and impulsivity are multicomponential—neither is a unitary construct, and so neither can be summarily described in terms of the two-process model without further differentiation. The subcomponents of attention, as well as of impulse control, develop dynamically, at different rates, integrating in different ways at different points in development, all reflecting the dynamic nature of neural maturation. In what ensues these component operations and their partially distinct neurobiology are noted. This is done via a taxonomic approach to the various functional domains at hand, as the discussion outlines the different types of regulation and their components relate them to development and to psychopathology.

Therefore, having outlined a fundamental heuristic model, and described the potential to locate developmental breakdowns in a handful of key processes, the essay can now consider in more depth the elements of attention and the elements of impulsivity *per se* and how they might develop or go awry in development.

ATTENTION: CONCEPTUAL FRAMEWORK AND KEY ADHD-RELATED EFFECTS

Definition

By classic definitions, attention refers to the facilitated processing of one source of information over another, although broad usages of the term can include capacity pool (Engle, 2002), as well as response readiness, arousal, regulation (Taylor, 1995), and other abilities (Mirsky & Duncan, 2001). With regard to mechanisms, as outlined by Yantis (1998), attentional selection can be based on spatial location (Eriksen & Hoffman, 1972), object features (Treisman & Gelade, 1980; Wolf, 1998), timing (Shapiro & Raymond, 1994), movement, or other object characteristics (Kahneman & Henik, 1981). Attentional selection is influenced by two overarching component functions, underscoring a dual-process theme: (1) bottom-up stimulus-driven processes that are relatively automatic and relatively early developing, and (2) top-down goal-driven processes that are strategic, relatively deliberate, related to the concept of executive control, and later developing. Consistent with the overarching framework used here, it has long been recognized that these two types of processes interact continuously, each placing constraints on the other (Schneider & Shiffrin, 1977). Researchers attempt to isolate these two influences in varying ways, depending on part on the age of the child. At the same time, as noted, often overlooked in the purely cognitive approaches to attention is the role of affective motivation in attentional allocation (Nigg & Casey, 2005; Pennington, 2002). Another limitation to this general formulation occurs in very early infancy. While one might see a semblance of exogenous versus endogenous attention in infants, top-down control supported by prefrontal cortex is not possible for very young infants. Their attention is governed by multiple processes, but these do not map neatly onto the two-process model.

However, even without considering emotion or infant development, the complexity of the cognitive component of attention alone has led to a massive literature that cannot be adequately captured in less than book length (de Fockert, 2013; Posner, 2004; Srinivasan, Thorpe, & Nunez, 2013). Highlighted here are certain aspects of attention that have been particularly influential in studies of attentional disorders and ADHD, that may be of most interest to students, or that suggest directions for the future.

Visual attention is the most well-understood modality of attention and therefore most often examined in developmental psychopathology. While not all aspects of visual attention generalize to auditory attention, a useful understanding of the principles of attention can be gained by considering results of visual attention studies and so they are the focus here.

Attention in the Brain

Turning to the brain, one recent perspective suggests six relevant and partially dissociable functional neural networks involved in attention. Figure 14.4 illustrates four of these putative cortical brain networks as recently synthesized from task-based and resting state functional brain imaging literature (Power et al., 2011) and consolidated recently by Petersen and Posner (2012) in an update of their earlier influential model of attention (Posner & Petersen, 1990).

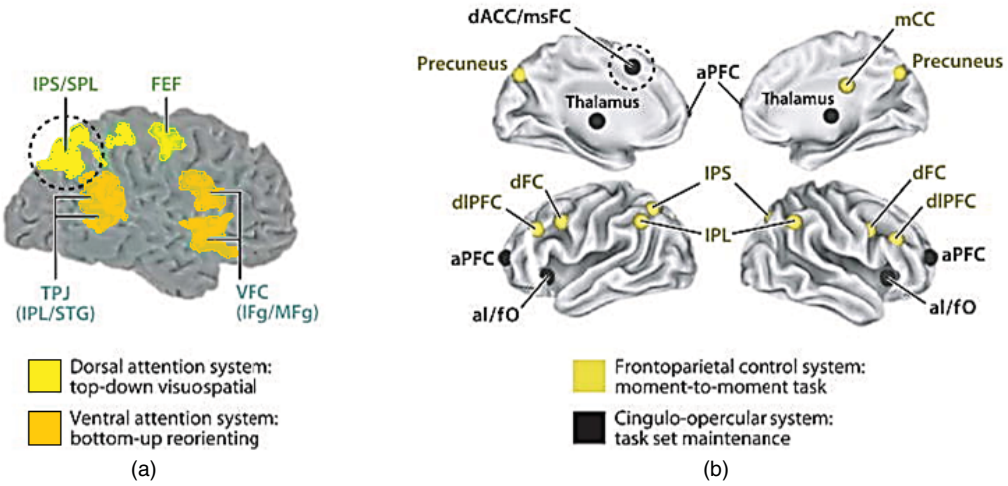


Figure 14.4 Brain attention networks. Panel a: Attention networks. The dorsal attention network = interparietal sulcus (IPS), frontal eye fields (FEF); it is associated with strategic direction of attention. The vental attention network includes temporal-parietal junction (TPJ), inferior frontal gyrus (IFG). It is associated with bottom-up capture of attention. Panel b: Executive control networks involved in higher order attentional allocation and control on task. Frontoparietal network includes dorsolateral PFC (dlpfc), IPS, medial cingulate (mCC); cingulo-opercular network includes dorsal anterior cingulate (dACC), anterior pole (aPFC), fronto-operculum (Al/fO), and thalamus as well as regions of striatum not shown. These canonical networks are inferred from functional connectivity as well as task based functional MRI data. For detailed discussion see Petersen & Posner (2012). See footnote 1. *Source:* Figure adapted with permission from Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annual Review of Neuroscience, 35*, page 76.

Panel (a) depicts two now well-recognized networks for the orienting of visual attention (Corbetta & Shulman, 2002). A dorsal frontoparietal network is engaged during top-down control of attention or goal-directed attention. It includes the frontal eye fields and interparietal sulcus (IPS). A ventral frontoparietal network is engaged during stimulus (or bottom-up) capture of attention and includes the temporoparietal junction (TPJ), the supramarginal gyrus, and inferior frontal gyus[3] (Chica, Bartolomeo, & Lupianez, 2013; Corbetta & Shulman, 2002; Thiebaut de Schotten et al., 2011). Note that while these two networks are well defined, an entire network does not inevitably activate in lock-step during all attentional tasks. For example, in the ventral network, TPJ and inferior frontal gyrus activation can be dissociated based on whether a novel stimulus is expected or unexpected (Shulman et al., 2009). Further, the top-down control of visual versus auditory attention likely share some features of attention (Petersen & Posner, 2012) but also differ somewhat anatomically with regard to perceptual signals. For example, while both involve middle and inferior frontal gyrus, the frontal eye fields are not as involved in auditory task control (Braga, Wilson, Sharp, Wise, & Leech, 2013). It is crucial to add that additional circuits or loci not shown here are engaged in attention, particularly when attention is motivated. These would include subcortical and basal ganglia brain regions as well as network-specific thalamic nuclei depending on the nature of the visual stimulus. Thus, the focus on cortical networks here is only part of the brain's overall engagement in attention.

The map to type 1 and type 2 processing for these two particular circuits is helpful yet rather incomplete. While most conceptions grant some degree of strategic control of attention to the dorsal network in the sense of endogenous orienting, the orienting systems are primarily involved in allocation of attention, but not more difficult control tasks like suppressing interference, handling response conflict, or complex working memory tasks. For these types of challenges we must invoke additional neural networks.

Experts disagree as to whether executive control is handled by one or two neural networks (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Petersen & Posner, 2012), but these perspectives do not dramatically change the story here. The perspective that argues for two such networks (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Petersen & Posner, 2012) proposes the following.

[3]Some renderings include the frontal operculum (Chica et al., 2013, as cited in text), but here I follow the version provided by Petersen and Posner (2012), who suggested differentiating the ventral network more fully from the fronto-opercular network.

As depicted in Figure 14.4, panel (b), there are two putative networks involved in executive functioning. In keeping with our model of hierarchical control in prefrontal cortex, these executive (or task-control) circuits are engaged when *complex* attentional strategies are needed. The frontal-parietal-task control network (depicted in yellow), which is more anterior to the dorsal attention network, includes the dorsolateral prefrontal cortex. Petersen and Posner (2012) propose that it is involved in initial task evaluation and engagement, although the hierarchical model described earlier might amend this to propose that it is engaged in working memory and other control tasks that do not require multi-level switching or context processing. The cingulo-opercular network (in black) includes the remaining regions usually associated with executive control including the lateral frontal pole, dorsal anterior cingulate, dorsolateral anterior prefrontal cortex, and anterior insula. Petersen and Posner (2012) proposed that it is involved in maintaining effort on a task and suppressing competing information. It may also be engaged in particularly difficult task switching paradigms, according to the hierarchical model. In other words, depending on task complexity, abstraction, and duration, type 2 processes or attention allocation will involve both the dorsal attention and one or both executive control networks.

Two other networks are important that are not shown in Figure 14.4. A so-called *default mode network* is also involved; it includes the posterior cingulate cortex, the ventromedial prefrontal cortex, lateral inferior parietal lobes, and medial temporal structures. Its functions are still debated, but it activates when task control is relaxed and de-activates when task control is engaged. Yet it also is active in many other task situations, so it may be important to some tasks such as determining the relative focus on internal and external stimuli, in retrieving autobiographical information, or in integrating recent experiences (Spreng, 2012). The posterior cingulate cortex in particular may be involved in regulating consistency of responding (Leech & Sharp, 2013) and so may be relevant to resource allocation and response variability, as discussed in subsequent sections. Notably, the default mode network appears to have altered connectivity in ADHD as well as other disorders (Fair et al., 2012). The final network is an alerting (or, in some conceptions, arousal) network, which is discussed subsequently under the section heading, *capacity*.

This multi-network model helps us heuristically think about the ADHD clinical picture. For example, a common clinical observation in ADHD is that the child cannot focus on their homework or on what they are being told to do (weak controlled attention), but they can focus for hours on an engaging videogame (attentional capture) while being unable to disengage from it upon instruction (weak controlled attention). Thus, the two-process/three-network model helps us resolve the superficial paradox of situational-specific attentional focus in children.

Brain Imaging, Attention, and ADHD

What do brain imaging and cognitive studies tell us about the integrity of attentional processes and their neural supports in ADHD? Numerous MRI findings have provided consistent evidence that at the group level, neural regions and networks associated with type 2 attention processes are altered in function or development in groups of children with ADHD (Bush, 2010; Durston, van Belle, & de Zeeuw, 2011; Rubia, 2011). Key findings from MRI studies of the brain in recent years are noted here, with an emphasis on meta-analytic findings when available. Then, studies of attention itself (not of brain function), conducted in the laboratory under controlled conditions, are considered in relation to ADHD.

Functional MRI studies are quite interesting in regard to the two-process model and the circuits just described. A meta-analysis (Cortese et al., 2012) covering data through 2011 identified 55 relevant functional MRI studies with a total of 741 ADHD and 801 comparison subjects. That meta-analysis unfortunately was quite limited in that it did not report effect sizes. However, it did conclude that ADHD was associated with abnormal (mostly hypoactivation) response in multiple brain nodes that are part of distinct brain circuits. While it relied on canonical networks suggested from a study of 1,000 adults (Yeo et al., 2011), these are similar to those described in Figure 14.4. Cortese et al. concluded that in addition to frontal-striatal circuitry, in children there was abnormal hypoactivation in the ventral attention network, while in adults there was abnormal hypoactivation in the dorsal attention network. These results were not explained by either comorbid conditions or treatment history. In addition, they highlighted that findings in a smaller number of studies related to hyperactivation of the default network as well as sensory networks (vision) and hypoactivation of motor networks that need further exploration. Again, it is important to point out that the method used in this analysis relied on so-called functional networks that are being explored in the brain using MRI; these are confined to cortical networks and do not represent thalamic, limbic, or other subcortical components of these and other networks in the brain.

A second meta-analysis took a different approach, enabling consideration of subcortical areas and thus filling

in a gap from the preceding study (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). They selected studies using task-based MRI that the authors considered to be measures of attention including divided attention tasks (e.g., oddball), sustained attention (e.g., continuous performance test), and flexible attention (e.g., mental rotation). The results are reproduced in part in Figure 14.5. They further highlight the role of breakdown in attention-related neural circuits in cortical areas, as well as bringing to bear the important subcortical components of attention control. The figure depicts that ADHD is associated with regional hypoactivation during attention tasks in key nodes of the frontoparietal task control network (notably, dorsolateral prefrontal cortex) and associated subcortical components of thalamo-cortical-striatal neural loops involved in cognitive control, including putamen, caudate, and portions of the thalamus. It also shows altered activation in the insula and inferior parietal lobe, in the precuneous, and increased activation in the left cuneus and right cerebellum.

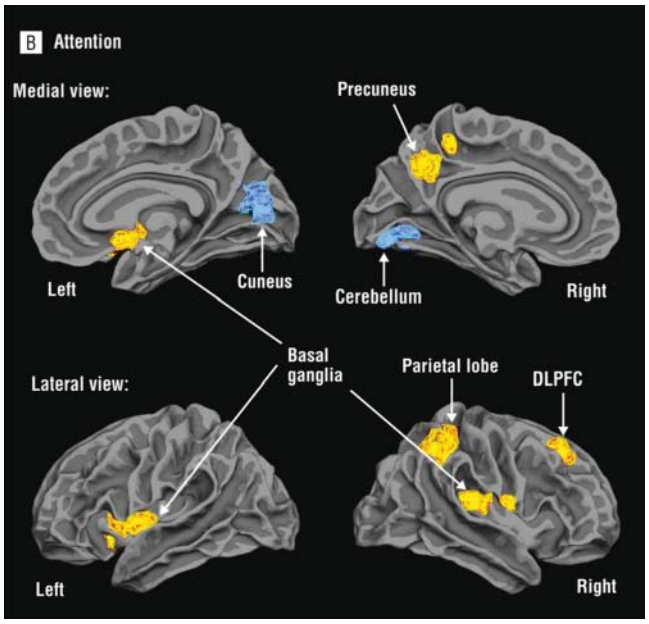


Figure 14.5 Altered brain activation during attention tasks in ADHD. ADHD associated on attention tasks with decreased activation in the right dorsolateral prefrontal cortex (DLPFC), left putamen and globus pallidus, right posterior thalamus (pulvinar) and caudate tail extending into the posterior insula, in the right inferior parietal lobe, and in the precuneus and superior temporal lobe. Increased activation in the left cuneus and in the right cerebellum. See footnote 1. *Source:* Adapted with permission from H. Hart, J. Radua, T. Nakao, D. Mataix-Cols, & K. Rubia (2013), Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: Exploring task-specific, stimulant medication, and age effects, *Journal of the American Medical Association Psychiatry, 70*(2), page 191.

Whenever we consider breakdowns in neural systems, we must recognize that they may be disrupted via their interconnecting pathways rather than their modular loci. For example the distributed loci of the dorsal and ventral attention networks are thought to be connected via long fiber connections that lie along the longitudinal fasciculus (Chica et al., 2013) and that speculatively may participate in connecting the distributed regions of these attentional networks. However, note that these fibers may also form connections for the executive control network (the fourth network shown earlier in Figure 14.4). Integrity of these long fiber connections can be queried using a different MRI technique called *diffusion tensor imaging* or DTI. DTI uses the molecular spin of ions to gauge direction of water or fluid flow in the brain; that flow tends to be directional where axons are well developed and diffuse where they are less developed. Leaving aside here several complexities in interpreting that signal, from a simplified point of view we can consider the degree of directional water flow as an index of axonal integrity at the level of white matter microstructure. Several studies have taken this approach with ADHD.

A meta-analysis is again helpful, pooling multiple studies of diffusion tensor signal (measuring white matter development) in ADHD children and adults. Although the collective database remains small (9 studies, 173 ADHD and 169 control participants from 5 to 49 years of age), one consistent finding in research on ADHD in the past decade has been alterations in white matter microstructure along the superior longitudinal fasciculus (van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). Figure 14.6 reproduces their key results. Findings that held across the pooled data are highlighted with blue coloring available online. Note the second column in the figure, showing effects for the right anterior corona radiata. This was the largest cluster found, and as the authors noted probably incudes parts of the superior longitudinal fasciculus, implicating altered development of fibers that support top-down control of attention via either the dorsal attention network or the frontal-parietal task control network. It was notable that there were stronger effects in younger children (Nagel et al., 2011), suggesting the potential to use this technique to map development of ADHD.

Laboratory Tests, Attention, and ADHD: Type 1 Attention

Laboratory tests of attention are illuminating but the literature is vast. Type 1 attentional regulation can be studied via experiments to assess reflexive orienting and perceptual selection, among others. Other experiments have tapped

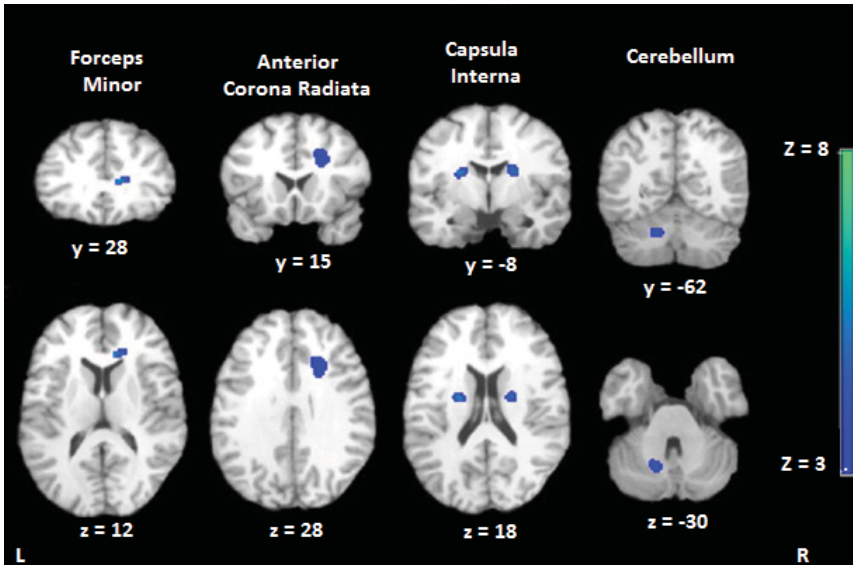


Figure 14.6 Figure 6: White matter microstructure and ADHD. Meta-analysis results for fractional anisotropy effects ADHD versus non-ADHD (all effects $z > 3$, $p < .05$ corrected). Top row: Coronal view. Bottom row: Axial few. L = Left, R = Right. See footnote 1. *Source:* Reprinted with permission from H. van Ewijk, D. J. Heslenfeld, M. P. Zwiers, J. K. Buitelaar, & J. Oosterlaan, (2012) Diffusion tensor imaging in attention deficit/hyperactivity disorder: A systematic review and meta-analysis, *Neuroscience & Biobehavioral Reviews, 36*, page 110.

type 2 attentional processes via strategic attentional orienting, late stage selection, task switching, working memory, and interference control tasks. Note that when it comes to type 2 processes, most of the ADHD-related literature involves tasks that engage the frontal-parietal network as well as the dorsal attention network, so clear conclusions isolating their involvement is difficult in both MRI and cognitive studies. Nonetheless, we can make several observations.

Perhaps the most fundamental type 1 process is orienting to an unexpected stimulus, called exogenous orienting and also sometimes referred to as covert orienting because it is nondeliberate and can occur without eye movement (Carrasco, 2011). A literature has examined ADHD on basic computerized visual orienting tasks to test this function, while a few studies have added ERP recordings as well. With regard to the basic orienting to a stimulus or cue, one early meta-analysis concluded that the salience network was operating normally in ADHD (Huang-Pollock & Nigg, 2003). However, the studies reviewed there failed to carefully distinguish unwarned alerting, an important function of attentional capture albeit one dependent on the state of arousal or capacity as much as on type 1 process per se. Studies using ERP to examine the early processing of cues seem to suggest that when failures are observed in exogenous orienting, they are best understood as driven by failures in alerting or failures in arousal (capacity) rather than in the targeted ventral system *per se* (Ortega, Lopez, Carrasco, Anllo-Vento, & Aboitiz, 2013). In particular, when confronted with unwarned targets, amplitude of ERP response (here, the negative signal at 100 ms or N-1 component) is weaker in ADHD than non-ADHD. Children with ADHD also under-respond to warning cues (here, the contingent negative variation or CNV signal) on ERP studies of orienting (Benikos & Johnstone, 2009). These findings can be interpreted either as failure of capacity or state readiness (arousal) or else failure of the salience network per se, although the cited authors tended to favor the former explanation. In an effort to sort out this ambiguity, Huang Pollock et al. (2006) combined results from a continuous performance task and an endogenous cueing or orienting task. They, too, concluded that exogenous orienting was spared but that alertness (arousal or capacity) was impaired. A similar conclusion was reached when alerting and endogenous orienting were isolated by task design in a study of adults with ADHD (Oberlin, Alford, & Marrocco, 2005).

Other task designs also seem to converge with this picture. With regard to selection, historically the data have argued against a perceptual selection (type 1 selection process) problem in ADHD (Berman, Douglas, & Barr, 1999; McIntyre, Blackwell, & Denton, 1978; Sergeant & van der Meere, 1988; Sharma, Halperin, Newcorn, & Wolf, 1991). A review of automatic versus effortful visual search concluded that children with ADHD have normal automatic (type I) visual search processes (Mullane & Klein,

2008). Many such investigations lacked systematic control of perceptual load in addition to other limitations, (see critique by Douglas, 1999). The issue of load in particular was a potentially important gap in light of subsequent theories of load and selection (Lavie, 1995). Yet, even when our group controlled perceptual load more systematically using newer paradigms, perceptual selection problems were not detected in ADHD-C (Huang-Pollock, et al., 2002). All of these findings suggest that, despite imaging findings, at the performance level it is difficult to identify marked problems in the ventral attention system itself—unless one attributes failures of alertness, arousal, or energy to the ventral network. I suggest that a resource capacity limitation in ADHD magnifies any weakness in the ventral attention system and is most parsimoniously understood as a capacity problem rather than a ventral attention problem.

In the face of evidence that type 1 processing of attention is not primarily involved in ADHD, theorists have suggested that the posterior attention network may be a mechanism in children in a *subgroup* with a refined ADHD inattentive type who are not hyperactive (Goodyear & Hynd, 1992; Milich, Balentine, & Lynam, 2001). Very few data address this possibility formally.

Yet there has been substantial concern in the nosology literature that the ADHD inattentive subtype (now presentation) may not be well-specified. In particular, it may be that items tapping sluggish cognitive tempo (a tendency of a child to be spacy, underactive rather than overactive, and have low energy) are important to recognize when defining a subgroup with purely inattentive forms of ADHD (Carlson & Mann, 2002; McBurnett, Pfiffner, & Frick, 2001). Indeed, in *DSM-IV* and *DSM-5*, the inattentive type/presentation includes children who are overactive (but just below the threshold for ADHD combined) plus children who are clearly underactive. The latter group may be those most affected by a posterior attention system dysfunction (Milich et al., 2001). An interesting possibility is that subgroups, based either on phenotype or genotype, show type 1 attention problems. Bellgrove et al. (2009) reported that genotype moderated deficits on an endogenous orienting task. Three other studies looked at children who were defined as inattentive without any hyperactivity—that is, a more restrictive definition than that provided by the *DSM-IV* subtypes or the *DSM-5* presentations.

Carr et al. (2010) used a relatively novel task called the attentional blink, in which rapidly presented stimuli cause an involuntary "blindness" to ensuing stimuli after a relevant target is presented. The idea is that for a couple of hundred milliseconds after detecting a target, attention lapses while the stimulus is verified and stored in memory. The "blink" is thought to reflect an automatic filtering mechanism. It was generally normal in ADHD but abnormal in the subgroup with pure inattention. This could reflect a type 1 process failure or a capacity failure. Goth Owens et al. (2010) used simple speed of output tasks, and found that speed was slower in the group with pure inattention. This result could suggest an energy deficit (capacity) unique to that group. A third study (Derefinko et al., 2008), similarly defining an inattentive type without any activity elevation, also saw alterations in cognition in this group that could reflect either type 1 processing or else capacity differences.

Laboratory Tests, Attention, and ADHD: Type 2 Attention

The most heavily studied domain of attention in ADHD is controlled attention, broadly defined. These studies include both strategic allocation of visual attention (the narrow definition confined to the dorsal attention network) and studies of task control (involving increasingly anterior portions of prefrontal cortex in the frontoparietal network). Numerous reviews and meta-analyses have demonstrated that compared with typically developing individuals, children and adults with ADHD have, as a group, worse performance on laboratory measures of cognitive control and executive functioning (Alderson, Kasper, Hudec, & Patros, 2013; Kasper, Alderson, & Hudec, 2012).

A key question concerns whether we can fractionate or isolate component abilities in relation to ADHD. As noted earlier, functional MRI studies of cognitive control in normal adults suggest that increasingly complex control tasks involve more anterior portions of frontal cortex. Recall the Badre and D'Esposito (2009) see "hierarchical model". Let us now consider it in more detail. Those authors suggested that dorsal premotor cortex (approximately Brodman's area 6) is involved in response selection, stimulus-response rule execution, and similar single-rule learning tasks. The premotor cortex and caudal prefrontal cortex (approximately area 8) engages when tasks are somewhat more complex, such as response-sequence selection, sequence categorization, and stimulus-response rule learning. Still more complex tasks involve the mid-dorsolateral prefrontal cortex (approximately areas 9/46), including task switching and maintaining cross-temporal contingencies. Finally, the most abstract tasks involve the frontal pole (area 10), including episodic goal monitoring and shifting from internal to external attention. Thus, by this perspective there is some potential value in isolating ADHD dysfunction if scientists could isolate what level of abstraction and what

modules in prefrontal cortex might be especially vulnerable to breakdown when individuals have symptoms of ADHD.

Without getting this specific, neuropsychological models have accordingly often suggested various fractionations of executive functions such as the distinction between working memory, set shifting, interference control (late selection and strategic orienting), and planning (e.g., Friedman & Miyake, 2004; Mirsky & Duncan, 2001; Miyake & Friedman, 2012; Miyake et al., 2000; Pennington & Ozonoff, 1996; Redick, Calvo, Gay, & Engle, 2011; Unsworth, Redick, Heitz, Broadway, & Engle, 2009). Despite this effort, cognitive and neuropsychological studies of ADHD have not yet established this level of precision, for two reasons. One reason is that the tasks used in ADHD studies remain too noisy to isolate neural circuits or psychological functions within the type 2 domain. The other is that individuals with ADHD are highly variable in their responding—itself an interesting observation discussed in the section on resource *capacity* below.

Nonetheless, attempts are beginning. For example, Rubia (2011) reviewed a series of studies from her laboratory that suggest that tasks of sustained and controlled attention differ in which portions of prefrontal cortex are differentially activated in ADHD versus control children, with the latter task type moving activation deficits closer to the frontal pole. More work of this nature that focuses specifically on effect sizes and on individual variation will set the stage for better clinical prediction.

The prior citations also suggest empirical and conceptual distinctions between inhibition, shifting, and working memory/updating. Working memory has been perhaps the most well operationalized aspect of controlled attention (Conway et al., 2005; Redick & Engle, 2011; Unsworth & Engle, 2007), even though a very wide range of measures have been labeled as working memory in studies of ADHD that sometimes confound short term storage with working memory. Working memory is theorized to have distinct elements. The first element, commonly referred to as the central executive (Baddeley & Hitch, 1994) or working memory capacity, is viewed as a domain general ability that essentially taps the same construct as the frontoparietal task network discussed earlier (Engle, 2002; Engle, 2001). It involves the ability to protect and manipulate information in mind, and likely depends in part on dorsolateral-prefrontal cortex (Kane & Engle, 2002). The second element entails domain-specific, short-term memory modules for temporarily holding information. The most common division of these is into the visual sketch pad (visual working memory) and the phonological loop (speech-based information or verbal working memory; (Baddeley & Hitch, 1994). Nearly three dozen experimental studies have looked at working memory and related abilities (short term memory, planning) in ADHD. These are most interpretable if sorted into verbal versus spatial domains. Meta-analytic data suggest that averaging across ages and tasks, children with ADHD differ from controls by about 0.7 standard deviations in terms of working memory (Kasper et al., 2012). However, this effect size may more than double when the focus is on tasks that have high memory load (e.g., dual task designs) and studies of younger children (e.g., age 8 years of age). The significant cognitive developmental shifts that occur from 5 to 8 years of age may be a period when children, particularly boys, with ADHD tend to lag their peers and fail to make a rapid consolidation of type 2 attentional processes (Kasper et al., 2012). A working memory weakness in ADHD also persists into adulthood (Alderson et al., 2013).

Higher level type 2 processing is often operationalized in tasks that are referred to as interference control (Barkley, 1997; Berger & Posner, 2000). The most classic such task is the Stroop task (MacLeod, 1991). One must name the ink color of color-words (e.g., the word red printed in green ink); reading the word is more automatic than naming the color, so interference results. Both qualitative (Nigg, 2001) and quantitative reviews (Homack & Riccio, 2004; van Mourik, Oosterlaan, & Sergeant, 2005) have concluded that Stroop interference is at most minimally impaired in ADHD. However, the null findings probably reflect methodological problems with the paper-and-pencil version of the Stroop task, which consistently reveal slow naming speed but not an additional interference effect (Nigg, 2001). Subsequent investigations have been somewhat more confirming of ADHD problems when using computerized interference control tasks, which prevent response strategy effects to which the paper stimuli had been vulnerable and also provide more precise timing measures (Assef, Capovilla, & Capovilla, 2007; Bush et al., 1999; Carter, Krener, Chaderjian, Northcutt, & Wolfe, 1995; Jonkman et al., 1999, but see Huang-Pollock, Nigg, & Carr, 2005).

Numerous other multicomponent tasks, including widely used clinical measures like the Trailmaking and Wisconsin Card Sort test, show modest effect size differences between children with ADHD and typically developing children (Willcutt et al., 2005). More contemporary studies of, for example, task switching that can truly tap the higher order control that engages the frontal pole and the task-control network, are needed to

clarify this picture. Some studies have begun to do so. For example task switching designs all induce a response set and then measure reaction times when the primary response set must be changed; they can monitor dual-task performance (performance cost of doing two things at once) or switching costs (see Pashler, 1998). Application of these more refined paradigms to ADHD has begun. Initial studies provide some evidence of rapid, controlled shifting deficits (Cepeda, Cepeda, & Kramer, 2000; Hollingsworth, McAuliffe, & Knowlton, 2001; Oosterlaan & Sergeant, 1998; Perchet, Revol, Fourneret, Mauguiere, & Garcia-Larrea, 2001; Rauch, Gold, & Schmitt, 2012; Schachar, Tannock, Marriott, & Logan, 1995), but studies to date are too few and varying in method to allow firm conclusions about whether the magnitude of the effect is larger here than for simpler control tasks, as the hierarchical model of frontal lobe activity and task complexity would predict.

Summary

Evidence for a problem in type 2 attention in ADHD exists from a wide range of neuropsychological investigations, although such deficits not large enough for clinical application as ADHD is currently defined. Newer, more refined measures of cognitive selection and working memory that capitalize on reliable reaction time measures that truly tap the complex attention implemented in the most anterior neural networks are likely to be most helpful in future evaluations.

Resource Capacity Limits and ADHD

Problems in energetic or resource state have been one central proposal for an ADHD mechanism (van der Meere, Börger, & Wierseman, 2010). Yet the definition of energetic state or capacity has been elusive in the literature. It can refer to effort pool, energy, arousal, attentional capacity, or motivation. Yet these are quite distinct constructs in terms of the intellectual traditions from which they derive and hence their connotations. An arousal perspective is adopted here, while briefly noting other approaches.

Arousal

Arousal is undeniably important to effective adaption; someone who is too lethargic cannot accomplish much, nor can someone who is panicked. Extreme lapses in the arousal function are salient in such medical conditions as epilepsy and narcolepsy. Arousal is to some extent involuntary—at a certain point, we fall asleep no matter how much we want to stay awake, or panic no matter how much we want to stay calm. Yet it also has some degree of voluntary regulation—by strategic planning we can relax a bit, by effort we can overcome our fatigue and continue on a boring task when weary. The classic Yerkes-Dodson curve describes optimal performance under optimal arousal. Developmentally, arousal is an important characteristic even in infants and is considered perhaps the earliest hallmark of self-regulation (Olson, 2002). Crucially, regulation of arousal from very early in life is heavily dependent on caregiver responsiveness. For example, a large body of literature notes the difficulty in arousal regulation experienced by children with insecure attachments to their parents when in stressful situations, and some evidence suggests that this relation is not merely temperament driven but is at least in part a reflection of the quality of the parent–child interaction (Olson, 2002; Schore, 1994). Similarly, early sleep regulation is partly temperamental and partly related to parental monitoring (Dahl, 1996; Peirano, Algarin, & Uauy, 2003). Whether these different examples of arousal are all addressing the same underlying processes is an open question but they clearly moderate other attention and impulse control operations. However, arousal has suffered historically from under-specification particularly in terms of neurobiology.

One influential integration comes from the same model guiding the discussion of attention herein from Posner and Petersen (Petersen & Posner, 2012; Posner & Petersen, 1990). They proposed that an arousal system, which they call *alerting*, is responsible for establishing and maintaining an alert state suitable to task demands and preferences. In this perspective, *vigilance* depends on a network of neural structures that include the noradrenergic system originating in the locus coeruleus, the cholinergic system of the basal forebrain, the intralaminar thalamic nuclei, the right prefrontal cortex (Parasuraman, Warm, & See, 1998; Posner & Petersen, 1990; Rothbart, Derryberry, & Posner, 1994), and the ascending reticular activating system ((Mirsky & Duncan, 2001) the latter is related to wakefulness). Peterson and Posner (1990) noted two distinct functions. The first was phasic *alerting* to a stimulus (Berger & Posner (2000); called arousal by Pribram & McGuinness, (1975), and stabilize by Mirsky & Duncan, (2001)). The second was tonic sustaining of attention to the stimulus, called *vigilance* (Posner & Peterson, 1990) or *sustained attention* (Mirsky & Duncan, 2001).

Posner and Peterson (1990) proposed that arousal (alerting) is a right brain lateralized process of activation by noradrenergic neurons. It responds to stimulus input

and prepares to take advantage of new information by enhancing the signal:noise ratio for novelty detection. Classic theories of ADHD emphasize a deficit in cortical arousal (Satterfield, Cantwell, & Satterfield, 1974; Zentall & Zentall, 1983) or, concomitantly, disruption in ascending noradrenergic neural systems that facilitate signal:noise detection (McCracken, 1991). A line of ongoing work in the EEG theta:beta ratio requires integration here and also relies on an arousal framework.

A revision of this model by Aston Jones and Cohen (Aston-Jones & Cohen, 2005) is integrated into Peterson and Posner's (2012) more recent summation. This perspective retains much of the earlier idea but formulates the functioning of the ascending NE system from the locus coeruleus in terms of allocation of attention or focus to a single task (efficient) versus a diffuse (exploratory) framework. The tonic-phasic terminology is retained but its function is clarified in computational terms. In this perspective, ascending NE systems are involved via projections to frontal and parietal cortices in bottom-up optimization of behavioral performance by influencing responsivity (a gain parameter) in those cortical systems. Meantime, downward projections from PFC can regulate the NE system, helping to explain how top-down cognitive control can be involved in deliberate regulation of arousal and task efficiency. The *phasic* activity is important in this efficient mode, as phasic NE firing is associated with task-relevant responses. The *tonic* mode is important to maintain general alertness, but when tonic activity is high and phasic activity is low, the person is distractible and aroused; when both are low, the person is drowsy and not alert. That proposal is obviously of interest for hypotheses about ADHD neurobiology.

Arousal can be assessed in several different ways as listed in Table 14.2. Performance on a sustained task of detecting rare targets (continuous performance test) yields a signal detection parameter *d*-prime (d'). Reaction time variability on two choice decision tasks can be decomposed into indicators of a gain parameter (interpreted as arousal here for simplicity, although some experts would not agree) and of a decision set point parameter, which may be analogous to the CPT log-beta parameter that is sometimes seen as index of activation or tonic firing (Sergeant et al., 1999). EEG and ERP components may also be informative.

TABLE 14.2 Arousal-Related Concepts

	Arousal	Vigilance
Other terms	Phasic alerting	Tonic vigilance
NE system	Phasic	Tonic
Behavior balance	Task focus efficiency	Distractible if no phasic exploration
Measure (putative)	*d*-prime (d')	log beta
	RT variability-gain	RT decision parameter
	Theta-beta ratio	Event modulation
	CNV	

While slow reaction times (RT) seem like an obvious indicator of low arousal, the pattern of *reaction time variability* may be even better. A careful analysis of the reaction time literature actually shows that reaction times are not consistently impaired in ADHD (Huang-Pollock & Nigg, 2003; Kofler et al., 2013) so much as a consistent pattern of high within-individual variability of responding (Leth-Steensen, Elbaz, & Douglas, 2000). To determine whether variability is an index of arousal/alertness or of something else requires fractionation of the RT signal. RT may vary over seconds, minutes, hours, days, or weeks or even years and each of these may be of some informational value in understanding psychopathology (Ram & Gerstorf, 2009).

The past decade's literature has seen considerable interest in reaction time (RT) variability as a key marker in ADHD (Epstein et al., 2011) as well as other conditions. However, the main focus of ADHD research has been on fluctuations that occur from minute to minute or second to second. Within this framework, several methods for decomposing RT variability have been proposed to try to isolate cognitive functions that are relevant.

One advantage of RT variability is it can be retrieved from almost any study that includes reaction time as a primary measure. Taking advantage of this, a recent meta-analysis was able to pull RT variability data from over 300 studies to gauge effect sizes in ADHD (Kofler et al., 2013). This review made several important conclusions. First, children with ADHD do not have deficits in terms of slow RT after taking into account RT variability, but they continue to have deficits in RT variability after accounting for slow RT. Second, the effect size for simple RT variability ($d = .76$) is similar to other effect sizes for measures of controlled attention or arousal in the literature, suggesting that RT variability is not a more sensitive measure of ADHD than other cognitive measures touted as key deficits. Interestingly, the effect was slightly larger in children with ADHD than other clinical disorders (differential $d = .25$), although the effect in ADHD tended to be smaller in adolescents and adults than in children.

It also appears that from the perspective of subdomains of ADHD, RT variability is heritable and shares genetic variance with symptoms of inattention (Kuntsi et al., 2013). Yet RT variability can be affected not just by arousal (reflecting, perhaps, phasic NE firing), but also by

decision making strategy (e.g., cautious or reckless), and attention (distraction) (reflecting, perhaps tonic NE firing). Therefore, clarifying what drives the effect is needed. Three different methods are extant in the literature relevant to ADHD.

One approach decomposes the RT distribution within each participant using Fourier transformation into variation at different hertz, in line with the idea that the nervous system also oscillates at several hertz simultaneously (Wang, 2010). One proposal is that ADHD variability is occurring at slow wave forms, equivalent to an occasional *lapse* of attention every several seconds (Mairena et al., 2012). This could conform to claims that malfunction of the default mode network in the brain is dysfunctional (Sonuga-Barke & Castellanos, 2007). A careful review of relevant literature disproved that particular formulation as seen in RT data; children with ADHD have variable responding at all frequencies studied so far (Karalunas, Huang-Pollock, & Nigg, 2013), but more examination of both attentional lapses and oscillation cycles using physiological measures may be informative.

The second approach is to separate the Gaussian and ex-Gaussian components of the reaction time distribution (Leth-Steensen, et al., 2000). This approach is depicted in Figure 14.7. It shows that the approach decomposes the distribution into the mean and standard deviation of the normally distributed portion, and then a function called *tau* that reflects the mean and standard deviation of the non-Gaussian portion of the reaction time distribution. If this is done for each individual, then these three parameters can be separately assessed using regular statistical approaches. This method suggests ADHD deficits in *tau* but there has been controversy over what *tau* means psychologically. Deficits in *tau* are consistent with a deficit in arousal, but alternative interpretations are possible.

A third approach is called the diffusion model (Ratcliff, 2006; Ratcliff & McKoon, 2008). Here an information-processing paradigm is used. The model decomposes (1) a gain parameter (v) (rate of information processing), (2) a decision boundary parameter (conservative versus hasty decision making, conceptually related to the log-beta parameter in signal detection analysis), which could be indicative of tonic NE firing as explained earlier, and (3) nondecision processes that add to the overall processing time. The diffusion model has an important advantage in that it takes into account accuracy as well as reaction time, and so can accommodate speed–accuracy tradeoffs that bedevil other methods. The model is explained in Figure 14.8. However, note that as presented here, it assumes a two-choice reaction time task and so is applied to a more specific kind of task challenge than the ex-Gaussian model. This model has only recently been applied to ADHD. The first such study on a sizable sample (Karalunas, Huang-Pollock, & Nigg, 2012) suggested that the ADHD effect on both the reaction time and the reaction time variability was accounted for by the information gain parameter. This is very important because it locates an ADHD deficit not in perception or motor speed but in cognitive processing, and because it simplifies a multicomponent analysis of RT and RT

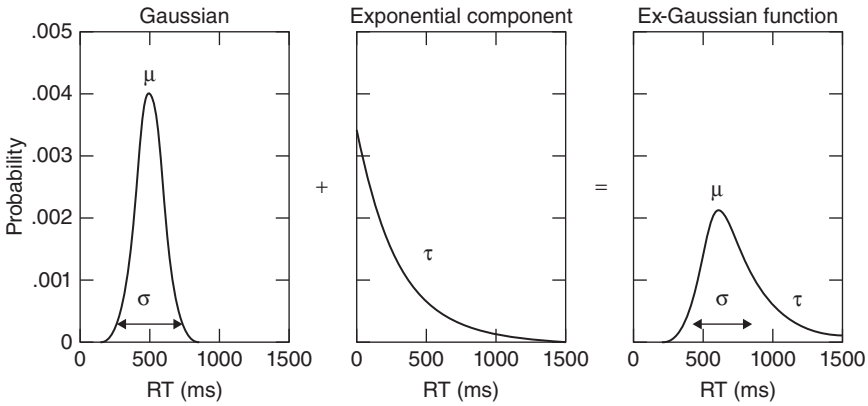


Figure 14.7 Ex-Gaussian decomposition of reaction time components. Reaction time distributions are usually positively skewed (third display on right), rendering a standard statistical analysis suspect. One solution is decomposing the distribution components. Left panel: μ reflects the mean of the normal (Gaussian) portion of the distribution, and σ captures the standard deviation of the normal portion of the distribution. Middle panel: τ reflects both the mean and standard deviation of the exponential portion of the distribution. Right panel: combining these describes the skewed distribution. *Source:* Used with permission and adapted from Karalunas, S. L., Geurts, H. M., Konrad, K., Bender, S., & Nigg, J. T. (2014). Annual Research Review: Reaction time variability in ADHD and autism spectrum disorders: measurement and mechanisms of a proposed trans-diagnostic phenotype. *Journal of Child Psychology and Psychiatry, and allied disciplines, 55*, page 707.

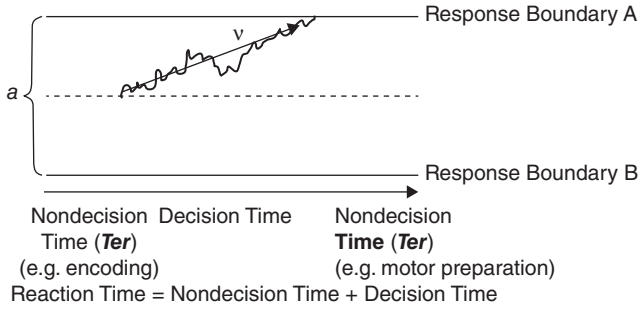


Figure 14.8 Diffusion decomposition of reaction time components. Drift rate (v) = rate at which information accumulates as reflected by the average slope of the line. It is determined by speed of information processing and noise (represented by the hypothetical jagged deviations from the average slope). Larger values of v indicate faster processing. Boundary separation (a) = conservativeness of the response criterion with wider separations indicating more conservative responding. Nondecision time (*Ter*) includes all nondecision processes, such as stimulus encoding and motor preparation. *Source:* Reprinted with permission from Karalunas, S. L., & Huang-Pollock, C. L. (2013). Integrating impairments in reaction time and executive function using a diffusion model framework. *Journal of Abnormal Child Psychology, 41*, page 839.

variability. If that result holds, it can likely be interpreted best as a weakness in capacity or arousal.

Other evidence is also consistent with this interpretation of RT variability in ADHD. Historically, the most widely used task for ADHD has been the continuous performance task (CPT). As noted earlier, a signal detection analysis can decompose the accuracy data to examine sensitivity to signal versus noise (most often used is one called *d*-prime or *d'*) see Table 14.2 in conjunction with decision bias (conservative or risky, for which one index is called log-β) (Lachman & Butterfield, 1979). It has been known for some time that ADHD is associated with poor signal detection (Losier, McGrath, & Klein, 1996).This finding can be interpreted as evidence of an arousal dysfunction.

Caveats to the arousal interpretation, however, were pointed out by van der Meere and colleagues (Sergeant, et al., 1999; van der Meere, 2002). They noted that most studies to that time (e.g., with the CPT) failed to consider *event rate* and that (1) failure to find sustained attention deficits on fast-event rate CPT tasks contradicts an arousal dysfunction hypothesis and thus (2) many of the performance data may in fact reflect a problem in activation (see later discussion). Moreover, (3) strategy effects (e.g., speed-for-accuracy trade-off) were often overlooked.

To address this criticism, a recent meta-analysis of 47 CPT studies considered both a signal detection approach (*d'*) and diffusion model to account for speed accuracy trade-offs (Huang-Pollock, Karalunas, Tam, & Moore, 2012) and also considered event rate variation across studies as well as estimating measurement artifacts. This thoroughly done analysis concluded that ADHD is associated with a deficit in *d'* of $d = .98$ (when seen from a signal detection lens), and in the information gain parameter $d = .75$ (seen from a diffusion modeling lens). Thus, these two approaches appear to converge in support of a deficit in capacity, likely in arousal although the arousal–activation distinction remains to be considered and is taken up again in the next section.

Another line of work related to low arousal in ADHD comes from EEG recordings. Among the first efforts to use contemporary definitions of ADHD and viable EEG methods was conducted by Satterfield and colleagues (Satterfield et al., 1974; Satterfield & Dawson, 1971). Recent electrophysiological work has often, though not unequivocally, been supportive (Brandeis et al., 1998; Monastra e al., 1999; Silberstein et al., 1998). The frequency or power spectrum of the EEG can serve as a central nervous system indicator of arousal (Minkwitz et al., 2011). Higher power in fast frequencies (e.g., the beta band) is seen as high arousal, while higher power in slow frequencies (e.g., theta band) is interpreted as low arousal (Arns, Conners, & Kraemer, 2012; Pizzagalli, 2007). The theta:beta ratio is often used to quantify arousal, although this interpretation has been questioned.

A salient finding in ADHD entails an excess theta:beta ratio, or excess relative slow wave activity. The literature on theta-beta ratio and ADHD has been meta-analyzed three times with different results. Boutros et al. (2005), using fairly liberal criteria for study inclusion, estimated an ADHD effect size of $d = .70$ for absolute theta power and of $d = 1.07$ for relative theta power. Snyder and Hall (2006) concluded that the theta:beta ratio was a startling 3.08; however that calculation was flawed by failure to use a pooled standard deviation when comparing group effects, as is considered best practice in meta-analyses (Borenstein, Hedges, Higgins, & Rothstein, 2009). Further, some studies with very large effects have had flawed methods, comparing their clinical group to norm groups obtained years earlier as noted by Arns et al. (2013). Arns et al. (2013) were more conservative, selecting a homogenous group of studies with similar protocols. They arrived at an effect size estimate of $d = .62$. They also noted a linear trend of decreasing effect sizes over time as additional studies are conducted. Thus, it appears that the EEG theta:beta measure performs similarly to other measures in differentiating ADHD from non-ADHD youth. Arns et al. concluded by emphasizing the potential prognostic value of the theta:beta ratio, which may help predict treatment response.

Activation

A complication for readers of the ADHD literature is that the concept of tonic vigilance is related in some models to still another older concept, that of activation (Pribram & McGuinness, 1975), a term itself often used in differing ways in the ADHD literature and in the developmental and temperament literature. The lack of isomorphism in handling activation across theories is related to distinct historical streams of thought (Strelau, 1994). One stream, exemplified by Gray (1982), arose from research on temperament and learning theory reaching back through the work of Eysenck to Pavlov's early conceptions of learning, in which activation was closely related to reward responding and thus to motivation. The second stream, exemplified by Posner and Peterson (1990) and Pribram and McGuinness (1975), arose from the cognitive sciences and information-processing approaches, which deemphasized incentive response and emphasized global response readiness and attention.

As a result, one historical thread of theorizing about ADHD has drawn on temperament and learning theory (and, more recently, associated animal models of ADHD), thus emphasizing reward response (Sagvolden, Aase, Zeiner, & Berger, 1998; Sagvolden, et al., 2005). Another thread of ADHD theorizing has drawn on cognitive and information-processing theory and emphasizes impaired demand-response preparation generally (e.g., Sergeant et al., 1999). A detailed summation of those historical perspectives was provided in the second edition of this volume (Nigg, Hinshaw, & Huang-Pollack, 2006), so only key points are noted here.

To distinguish these two meanings of activation is important. The reward-based activation concept is related to dopaminergic reward-learning circuits, whereas the vigilance system under discussion in this section is related to noradrenergic projections. I consider activation as a demand-response function in the current section, and as reward and incentive responding in the section on impulsivity later.

Traditionally researchers in ADHD have been interested in a concept of sustained attention or functioning against time on task. Time-on-task effects, however, have never been persuasive as a major deficit in ADHD because ADHD-related task-performance problems tend to appear rather quickly when placed under cognitive load. Tucker and Williamson (1984) recast the time-on-task domain as *activation* with an emphasis on motor preparation rather than attention. When activation is viewed in this way, evidence is more supportive of an ADHD-related deficit. Dutch scientists using time-on-task and event rate data reported that children with ADHD show normalized performance at medium event rates but weaknesses at slow and fast event rates on CPT (van der Meere, Shalev, Borger, & Gross-Tsur, 1995) and go/no go tasks (Borger & van der Meere, 2000; van der Meere & Stemerdink, 1999), leading these investigators to favor an underactivation explanation of ADHD cognitive and performance deficits (Sergeant, et al., 1999; van der Meere, et al., 2010). In other words, varying the rate at which a computer presents stimuli can moderate and nearly normalize response accuracy for children with ADHD.

A meta-analysis of event rate effects on a go/no-go task confirms that ADHD response parameters are markedly influenced by the event rate (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). That study showed that an ADHD deficit on the go/no-go task is not fully explained by event rate but is significantly moderated by it. ADHD slowing of reaction time was greater at slow event rates than at more activating fast event rates. Further evidence for a deficit in activation comes from the difficulty children with ADHD have in producing rapid motor responses over time (Carte, Nigg, & Hinshaw, 1996). In addition, some physiological data, in particular heart rate data, appear to be supportive (van der Meere, 2002).

Caveats to this argument entail failure of some activation predictions, versus arousal. For example, deficits on the CPT beta parameter (an index of response bias, that is, risky versus conservative) have not been confirmed in meta-analyses (Huang-Pollock et al., 2012; Karalunas, et al., 2012; Losier, et al., 1996). On balance, however, an activation dysfunction in ADHD remains an important possibility, with evidence of context-dependent functional deficits in children with ADHD requiring explanation.

Summary of Attention Section

Despite isolated neuroimaging data implicating brain regions in the ventral attention network, most evidence suggests that problems in a salience network or attentional capture process are not central to ADHD in aggregate. The picture may change when considering a subset of children who are sluggish and inattentive but it is too early to draw that conclusion. Instead, what appear as alerting or attentional capture problems appear to be better understood as problems not in type 1 attention, but in allocation of resources, via a problem in phasic arousal or, alternatively, tonic activation. Children with ADHD tend to have low arousal or low energy capacity to respond to tasks, reflected in signal detection and reaction time patterns as well as in physiological measures. Meantime,

type 2 attention is clearly affected in ADHD. The question is why those effect sizes remain modest: whether due to massive heterogeneity in ADHD children, to failure to use sufficiently difficult tasks that reach the top of the task hierarchy and demand full engagement of the executive networks in the brain, or to other reasons. I return to this point later when I consider future directions.

IMPULSE CONTROL: CONCEPTUAL FRAMEWORK AND KEY ADHD EFFECTS

Like attention, impulsivity is not unitary but involves multiple behavioral and neural systems, in addition to the interpersonal and incentive context in which the child is acting. When considering impulsivity measured by behavioral ratings of personality, for example, investigators find multiple dimensions.

Whiteside and Lynam (2001) conducted a factor analysis of numerous rating scale measures of related constructs (e.g., impulsivity, behavioral inhibition, sensation seeking) in adults. They identified four dimensions: (1) sensation seeking; (2) urgency (tendency to act rashly when distressed, also called by others negative urgency); (3) lack of planning; and (4) lack of perseverance (Whiteside & Lynam, 2003). Zapolski et al. (2010) confirmed a similar structure in children. These dimensions are not highly intercorrelated, consistent with other personality data that aspects of impulsivity are carried across different personality traits like extraversion (which includes a facet for sensation seeking), conscientiousness (facets for planning and persistence), and neuroticism. Thus, consideration of affective and nonaffective components of impulsivity and of the intersection with cognitive and stylistic tendencies in personality suggests a multifaceted construct.

In the experimental and laboratory measurement domain, then, it is not surprising that we see distinct approaches that are probably tapping different aspects of the everyday definition of impulsivity as a disposition to rash action. Reflecting this, two major frameworks or aspects of impulsivity have guided thinking in this area experimentally.

The first framework focuses on regulation of the impulse—how are impulses contained, stopped, or interrupted? Here, an impulsive action is seen as a hasty (stimulus-driven) action that was not adequately interrupted, resulting in doing what I did not want to do. The second framework focuses on decision making—how incentives are weighted, such that poor immediate rewards get chosen over superior but delayed rewards, with the result that I choose what I ultimately do not want as much (Ainslee, 2001). An impulsive action from this perspective is seen as one in which the ill-advised (that is, ultimately not desired) immediate option was preferred to the better (ultimately more desired), later option through a process of extreme *temporal discounting*. This second perspective intersects with the growing field of neuroeconomics.

Consider first the inhibition perspective. Here, within the child, I can simplify the descriptive options for a moment by considering again the deceptively simple question: How does a behavior (an impulse or a response that was about to be carried out) get stopped, interrupted, suppressed, or inhibited? Developmental studies suggest that either (1) more than one process is involved in controlling impulses in this way, or (2) an underlying control mechanism becomes able to interrupt different kinds of behavior at different points in development. For example, Dempster (1993) noted that the ability of children to suppress or inhibit motor movements develops earlier than the ability to suppress or inhibit word meanings in language use, although whether this is due to the differential rates at which motor and language skills develop or to distinct control operations coming online is uncertain.

Consider further that impulses can arise in at least two basic ways using our type 1 and type 2 process perspective. The type 1 action operates via an immediate incentive (reaction) that invites approach; type 2 action operates via memory of a long-term goal that comprises a series of next steps (strategic planning) and preidentified or learned steps. Correspondingly, impulses to action (motor or vocal response) are *controlled* by both top-down and bottom-up processes (Eisenberg et al., 2004; Nigg, 2001; Rothbart & Bates, 1998; Valiente et al., 2003). To achieve an important goal, one might overcome fear of a possible punishment (a new professor anxious about speaking in front of colleagues does so anyway to explain his work) exemplifying a top-down process. At the same time, anxiety might interrupt deliberate processes (the new professor forgets his next point due to the intrusion of a worry about how the talk is going), exemplifying a bottom-up process.

Affective processes thus can both trigger impulsive responding (negative urgency), or interrupt an impulse (anxious stopping of behavior). In the prior edition of this volume my colleagues and I provided a detailed description of bottom-up behavioral inhibition, derived from related lines of thought emanating from work by Jeffrey Gray and work by Jerome Kagan (Nigg, Hinshaw, & Huang-Pollock, 2006; Nigg, 2000b, 2001). Those related lines of work each suggest an important role for negative affect in both stimulating and interrupting impulsive behavior.

In this way, reward responding can also be seen as affectively driven source of impulse. From this perspective it is anchored in ascending dopaminergic systems in the brain, as also noted in the prior edition of this volume (Nigg, Hinshaw, & Huang-Pollock, 2006). Because those concepts are explained in detail in there, herein I focus on a different aspect of type 1 processing and impulsivity: temporal discounting of reward, which has dominated this literature in relation to ADHD and substance abuse recently and so is timely to review in this edition of the handbook.

Impulsivity and Type 1 Processes: Temporal Discounting of Reward and ADHD

One primary approach to studying impulsivity currently has been using the study of reward discounting—a research area which, while noted in economics since the nineteenth century and a focus of experimental study in psychology for over 40 years, has exploded exponentially, particularly in relation to psychopathology, in the decade since the prior publication of this volume. This approach, widely used in the substance abuse field to study decision making in relation to craving, has been surprisingly little utilized in attention-deficit disorders. This is despite the fact that ADHD confers elevated risk of future drug addiction. Therefore highlighting it can also serve to stimulate more work in that area.

The fundamental phenomenon here can be understood by asking whether you would prefer a modestly appealing option now or a more appealing option later, or whether you would endure an unappealing option now to reach an appealing option later. In a classic example (Rachlin & Jones, 2010), the alcoholic prefers being sober and healthy to being drunk and sick in the long run, but in the next 5 minutes he or she prefers to have a drink than not to have one. If the long-term pay-off always wins, he or she stays sober; if the short term one always wins, he or she is constantly drinking. In an experimental case, a neuroeconomist can ask whether you would prefer to have $10 now or $100 tomorrow. As with other impulse control disorders such as addiction or compulsive gambling (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012), in the case of ADHD it is fairly straightforward to demonstrate a group effect of excess preference for smaller sooner over later bigger rewards (Antrop et al., 2006; Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2012; Paloyelis, Asherson, Mehta, Faraone, & Kuntsi, 2010; Scheres, Tontsch, Thoeny, & Kaczkurkin, 2010; Wilson, Mitchell, Musser, Schmitt, & Nigg, 2011).

While the posing of the question experimentally implies that some reflection is involved, and while deliberate self-control clearly can override one's temporal preferences, the supposition in this theoretical approach is that these discounting computations are rather automatic as people make moment to moment choices. The symmetry in human and animal decision making paradigms, even in rodents and pigeons (noted below) supports this assumption of a type 1 process. Key questions concern how to best quantify discounting, how to use it to measure individual differences, how to define the phenotype so as to go after brain and gene correlates in development, and how to explain the phenomenon psychologically and biologically.

All of this has led to extensive new work on the discounting function, a function of considerable theoretical importance in ADHD (Sagvolden, et al., 1998). By progressively longer delays of the larger reward (how about in 2 days, 2 weeks, 2 months, 2 years?) the experimenter finds the *point of indifference* for that individual—how much time delay balances the value of the small and large payoff. This provides a precise quantification of the degree to which discounting occurs for that person. Of course, negative consequences (loss of reward) are also discounted—a punishment to occur in 10 years is not as concerning as one that will occur later today (think of how frequently people sign up for a balloon-payment mortgage). Discounting occurs not just over time, but also over probability or certainty of outcome, but it is not clear whether the same mechanism undergirds both kinds of discounting—an individual may discount more steeply for time than for probability or vice versa (Green & Myerson, 2013). This important complexity has not been much considered in work on ADHD.

In any event, the degree of preference for each reward (or outcome) over time can be captured by various mathematical functions, of which the most commonly supported is a now-characteristic hyperbolic function (Ainslee, 2001; Blackburn & El-Deredy, 2013):

$$V_d = A/1 + kd'$$

where V_d is the discounted present value of the future reward (e.g., $100 in a year is equal to $10 today), A is the reward amount, d is the delay period, and k is the discounting rate. This function is illustrated schematically in Figure 14.9 (Bickel, et al., 2012). Researchers typically solve for k, or else simply compute the area under the curve for the plotted function to compare different

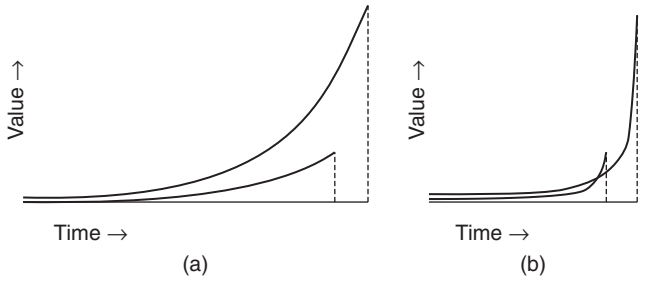


Figure 14.9 Temporal discounting hypothetical curve in addiction. This figure shows the predicted values of two reinforcers as a function of the delay until their receipt as predicted by the exponential model (left panel, A) and hyperbolic model (right pane, B). The height of the vertical lines represents the magnitude of subjective value on the future reward. *Source:* Reprinted with permission from W. K. Bickel, D. P. Jarmolowicz, E. T. Mueller, M. N. Koffarnus, & K. M. Gatchalian, (2012) Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: Emerging evidence, *Pharmacology & Therapeutics, 13*, page 289.

groups, as recommended by Madden & Bickel (2010) as well as Myerson, et al. (2001). The nuances of the difference between the *logical* exponential function and the *actual hyperbolic* function are intriguing with regard to the meaning of human cognition and how it handles uncertainty, but I bypass those here. However, note that accounting for differences in the slope function in clinical and normative samples is an important target in the field regardless of which shape is best fit to the data. A key advantage of the paradigm is the ability to translate it to animals, and one source of support for the conclusion of a hyperbolic discount function is that the same function appears in both animals (most commonly rats and pigeons) and humans.[4]

The neurobiology of discounting is relevant. When it comes to impulsivity, much of the classic impulsivity literature has emphasized the importance of serotonin systems on impulsive aggression and its relation to anxiety, mood, and impulsive behavior generally, but generally from the perspective of inhibitory control (next section), rather than discounting of reward (Apter, Plutchik, & van Praag, 1993; Coscina, 1997; Depue & Spoont, 1986). When it comes to reward discounting, emphasis has been placed on the role of dopamine functioning (Gianotti, Figner, Ebstein, & Knoch, 2012), and its importance in enhancing reward salience, particularly striatal-cortical dopamine projections. Important regions include the nucleus accumbens (ventral striatum) and medial and orbital-frontal regions of prefrontal cortex. An integrated understanding of the neurobiology of impulsivity will naturally integrate the role of both neurotransmitters along with norepinephrine, which also has important regulatory projections to PFC (Dalley, Mar, Economidou, & Robbins, 2008) as discussed earlier under the section on *capacity* and *arousal*.

The steepened slope of discounting function has been extensively studied in relation to drug addiction, but much less so in ADHD, despite a substantial literature in ADHD animal models and extensive theorizing on this gradient in relation to ADHD by leaders in the ADHD field (Sagvolden, et al., 2005).

Extensive reviews of simple two choice paradigms have concluded that ADHD is associated with some alteration in reward processing, typically preferring a small immediate reward to a delayed larger reward (Antrop, et al., 2006; Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2009; Marco et al., 2009; Paloyelis, Asherson, & Kuntsi, 2009; Tripp & Alsop, 2001); for a review see (Luman, Oosterlaan, & Sergeant, 2005).

However, the slope of the discount function cannot be estimated in a simple two-choice procedure, leaving the findings open to alternative explanations such as aversion to delay. Only a few studies have examined ADHD using the insights from the discounting perspective. In part this is rarely studied because children's cognitive limitations make it more difficult to implement the experimental paradigms involved in choice discounting paradigms. However, with some caveats, they tend to show the expected alteration in discounting function in ADHD. Barkley, Edwards, Laneri, Fletcher, and Metevia (2001) compared adolescents (aged 12 to 19 years) with ADHD and comorbid oppositional defiant disorder (ODD) to controls. The ADHD group displayed steeper discounting of delayed hypothetical rewards of $100 but not $1,000 when delays were between 1 month and 10 years. Scheres, Lee, and Sumiya (2006; 2008) found an association in college students between steepness of the discounting gradient and symptoms of hyperactivity/impulsivity, but not inattention, when rewards were real, but not when they were hypothetical. Paloyelis and colleagues (2009) found that

[4]One caveat must be noted. Whereas a reward is a desired object that motivates approach, a reinforcer is an outcome contingent on behavior that increases the likelihood that the behavior will reoccur. Not all rewards function as reinforcers, and not all reinforcers are rewards. Strictly speaking, most animal studies examine reinforcers, while human studies usually examine rewards. However, the expectation is that the dysfunction of reinforcement processes, which result in steeper discounting gradients observed in experiential procedures used with animals, will be captured also using procedures assessing delay discounting in humans.

preference for immediate rewards using a single-delay task design was positively related to ratings of inattention in children (average 8.8 years old). Neither of those child studies examined individuals with an ADHD diagnosis, however.

Scheres and colleagues (2006) found no difference in delay discounting in children and adolescents with ADHD and matched controls using an experiential task with actual rewards up to $0.10 using very short delays (up to 30 seconds). However, in their next study (Scheres, et al., 2010), using three delayed reward amounts and delays up to one minute, again in a sample of 6–17-year-olds with and without ADHD, found steeper delay discounting among participants with ADHD.

Only one other study has examined subjective value across longer delays in ADHD or looked exclusively at preadolescent children with ADHD. In that study, Wilson et al. (2011) estimated discount function, compared children with ADHD and typically developing children aged 7–11 years on a hypothetical discounting choice task in which children were given a pairing of different short and long term hypothetical rewards and discounting curves were computed. Their results are shown in Figure 14.10, illustrating the classic fit of the hyperbolic function and showing the steeper discounting in ADHD. Using a subset of that sample, Cost-Dias et al. (2013) conducted functional connectivity using resting state MRI, and showed an association of the discounting function with increased connectivity from the nucleus accumbens to prefrontal cortex—a finding that fits well with conceptions

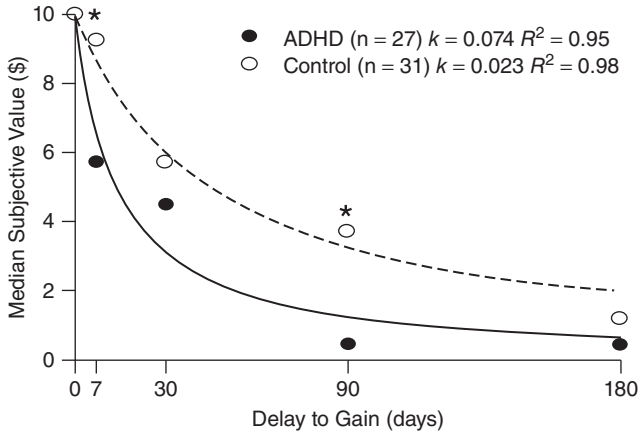


Figure 14.10 Temporal discounting curve in children with ADHD and typically developing control children. *Source:* Reprinted with permission from V. B. Wilson, S. H. Mitchell, E. D. Musser, C. F. Schmitt, & J. Nigg, (2011) Delay discounting of reward in ADHD: Application in young children, *Journal of Child Psychology and Psychiatry, 52*, page 260.

of the neurobiology of the dopamine circuits involved in reward-related decision making.

Similar behavioral findings were reported by Demurie et al. (2012) for a sample of 8–16-year-old children. Notably, they also distinguished children with ADHD from those with autism spectrum disorder, suggesting some specificity to ADHD. Thus, it appears that the field is beginning to consistently describe a group effect in ADHD, confirming a discounting function in this population similar to what is seen in substance addiction.

Still, more definitive work is needed. For one thing, the issue of domain generality of effects (money, versus other incentives) has barely begun to be investigated in ADHD (Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2013). For another, the relation to other cognitive abilities, including IQ, needs further examination to understand the structure of cognition and decision making in ADHD. A proliferation of explanatory ideas related to ADHD deficit and reward function has not been matched by experimental studies that would differentiate different explanations for the phenomenon (Luman, Tripp, & Scheres, 2010).

Impulsivity and Type 2 Processes: Response Inhibition and ADHD

The second general control process is characterized by the involvement of strategic (i.e., deliberate, long-term) responses to events and their relation to long-term goals, closely connected to the now familiar construct of executive functions. This type of control can thus be termed executive or deliberate response suppression (referred to as executive inhibition in (Nigg, 2000b). It refers to the deliberate suppression of a response to achieve a later, internally represented goal (e.g., not scratching a mosquito bite so that it will heal faster; managing not to interrupt a long-winded colleague so as to fulfill a personal resolution to be more patient). Neurally, the specific suppression of a prepared or triggered motor response for strategic reasons (a hallmark of cognitive control) is related to a well-described brain network that includes the prefrontal cortex (in particular, orbitoprefrontal and right inferior frontal, especially inferior frontal gyrus (Aron, et al., 2003), basal ganglia (especially the caudate), and thalamus (Alexander, Crutcher, & DeLong, 1990; Middleton & Strick, 2002). It is modulated by frontal-cerebellar loops throughout development (Diamond, 2000; Middleton & Strick, 2001).

Convergence of approaches in describing the executive control system is apparent, given that deliberate or effortful

control of responding is emphasized in theories of both early cognitive development (Zelazo, et al., 2003) and early social-emotional development (Murray & Kochanska, 2002). However, these approaches have not yet been fully applied to the development of risk for ADHD. For example, surprisingly little research has considered *temperament antecedents* or *personality outcomes* in relation to ADHD (Nigg, Goldsmith, & Sachek, 2004; Olson, 2002; Sanson, Smart, Prior, & Oberklaid, 1993).

Yet the few studies to do so are quite consistent in suggesting that a broadly defined deliberate control domain (usually studied as *conscientiousness* in adults, or as *effortful control* in children) is associated with ADHD symptoms in preschool children (Goldsmith, Lemery, & Essex, 2004), school-age children (De Pauw & Mervielde, 2011; Martel, Goth-Owens, Martinez-Torteya, & Nigg, 2010; Martel, Nigg, & Lucas, 2008; Martel, Nikolas, Jernigan, Friderici, & Nigg, 2010), and adults (McKinney, Canu, & Schneider, 2013; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002; Nigg et al., 2002; van Dijk, Lappenschaar, Kan, Verkes, & Buitelaar, 2012).

Once again, we must consider more than two basic processes when considering response inhibition. Several proposals for fractionating strategic response suppression or inhibition are extant. For example: (1) stopping a primary, intended response on the basis of new information; (2) suppressing a competing and never intended response; or (3) inhibiting a reflex response that may be construed as distinct or similar, depending on the conceptual framework (Bari & Robbins, 2013; Barkley, 1997; Friedman & Miyake, 2004; Miyake et al., 2000; Nigg, 2000a).

The most influential model of response suppression on research about ADHD entails the interrupting of a prepared response before it was executed. Functional connectivity studies (Duann, Ide, Luo, & Li, 2009), while not without controversy, are supported by animal studies that again seem to confirm that a neural network involving basal ganglia, thalamic nuclei, and right inferior frontal cortex is involved in this ability (Aron & Poldrack, 2005; Bari & Robbins, 2013) as depicted in Figure 14.11.

Many tasks are used to assess this ability, such as the oculomotor antisaccade task and the go/no-go task. The formal model, assessed by a task called the stop task, was developed by Logan and colleagues (1984) and extended to work on ADHD by Schachar, Logan, and Tannock (Schachar et al., 1995; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989). This model is illustrated in Figure 14.12. It proposes that independent psychological and physiological processes are involved in triggering and executing a response (measured by go reaction time or

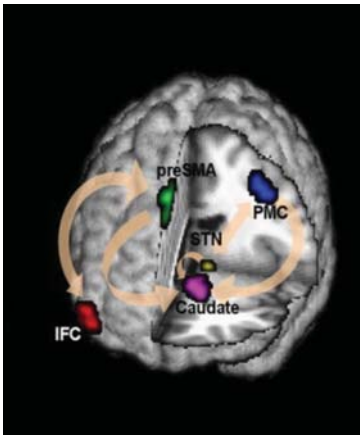


Figure 14.11 Brain model of response inhibition. Response inhibition has been mapped through a series of animal and human studies. The network now considered to be involved includes the subthalamic nucleus (STN), caudate, premotor cortex (PMC), presupplemental motor area, and inferior frontal cortex (IFC) and their interconnecting white matter tracts. See footnote 1. *Source:* Reprinted with permission from A. Bari & T. W. Robbins (2013) Inhibition and impulsivity: Behavioral and neural basis of response control, *Progress in Neurobiology, 108, 62*; and J. R. Duann, J. S. Ide, X. Luo, & C. S. Li, Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition (2009) *Journal of Neuroscience, 29*, page 10176.

Go RT, depicted in the top process in the figure) versus interrupting or stopping that response (measured by stop signal reaction time or SSRT, in the second process in the figure). The two processes race; whether or not the action is executed depends on the relative speed of the two processes. The everyday paradigm is the check swing in baseball: the batter begins to swing at the pitch and then interrupts the swing as the pitch breaks wide of the plate. The interrupt process is initiated after the go process (Figure 14.12) and has to catch up to it to stop the response from going forward. The delay after the pitch is thrown and the swing is begun until the warning not to go (the pitch begins to break) is the stop signal delay or SSD in Figure 14.12. With enough warning, the triggered motor response can still be interrupted.

This stop task accordingly uses varied timing of warnings to evaluate how much time individuals need to interrupt a response they were about to make. It has performed well in simulation studies (Band, van der Molen, & Logan, 2003). The concepts underneath this model also have found considerable support. For example, animal neuroscience data suggests distinct brain regions are involved in executing versus withholding a response (Baxter, Bucci, Holland, & Gallagher, 1999; Chiba, Bucci,

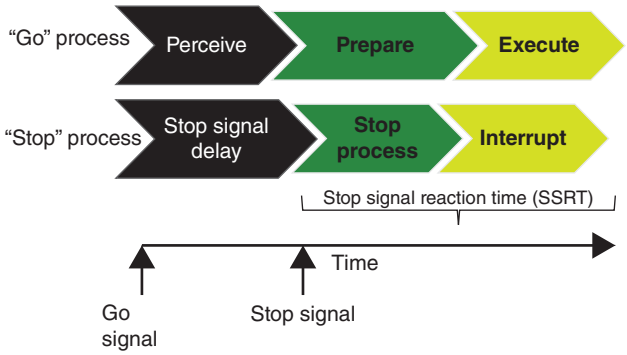


Figure 14.12 Race model of response inhibition. Two processes compete in this model. The go process launches when the go signal is perceived; the stop process launches when the stop signal is perceived. Depending on the timing of the stop signal and the speed of the two processes, the response will be executed or interrupted. SSRT = Go RT minus stop signal delay. The relative speed of the component processes is illustrative only and not to scale.

Holland, & Gallagher, 1995). Single electrode recording studies in nonhuman primates suggest that a specific inhibition activity operates centrally when stopping a response (Hanes, Patterson, & Schall, 1998; Hanes & Schall, 1995). The fundamental idea is that a disorder like ADHD, or any major impulse control disorder, is influenced by a too slow stop process or a very fast go process or both. Because it is already known that children with ADHD are unusually slow when executing fast actions, the primary hypothesis now is that they are even slower in their stop process. Accordingly in human children, efforts are made to measure the warning time needed so as to estimate the speed of the physiological stop signal. Dozens of studies in this vein suggest that children with ADHD have slower stop signal speed than typically developing children (Alderson et al., 2013; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Thus, this measure of response inhibition is among the most well established correlates of ADHD in the field.

However, one can question the mechanism behind that observation. This is in part due to other aspects of the data, and in part because of uncertainty about the meaning of the imputed stop signal reaction time under different data properties. The stopping process cannot be directly measured behaviorally, because nothing happens—the response does not occur. Instead it has to be inferred; for example in Figure 14.12, the warning delay is subtracted from average response time to estimate speed of stopping process. One problem is that because the stopping process is estimated, it has been unclear to what extent different methods of estimating will distort results due to reliance on assumptions about the distribution of responses (Verbruggen, Chambers, & Logan, 2013). This leads to the second issue, which is that the variability of the stop process cannot be estimated. In turn, psychometric inferences about the nature of the stop process are limited. Recent work suggests possible solutions to this problem (Matzke, Dolan, Logan, Brown, & Wagenmakers, 2012). Meantime, the race model of stopping is a viable way to model response interruption conceptually, but clinical application will require further work to evaluate psychometric properties of specific task implementations.

Indeed, neuroimaging studies using versions of stop and go/no-go tasks have been productive in clarifying the ADHD-related weakness in response inhibition. Rubia et al. (2013) also conducted a meta-analysis of response inhibition studies that used fMRI. The tasks they included were the stop task and go/no-go to index motor response inhibition, and Simon, Flanker and Stroop tasks to index interference inhibition (the latter is, arguably, as much a measure of attention as of inhibition). Those results are reproduced in part in Figure 14.13. They reveal altered activation in these tasks in children with ADHD, including effects in the insula, supplemental motor area, anterior

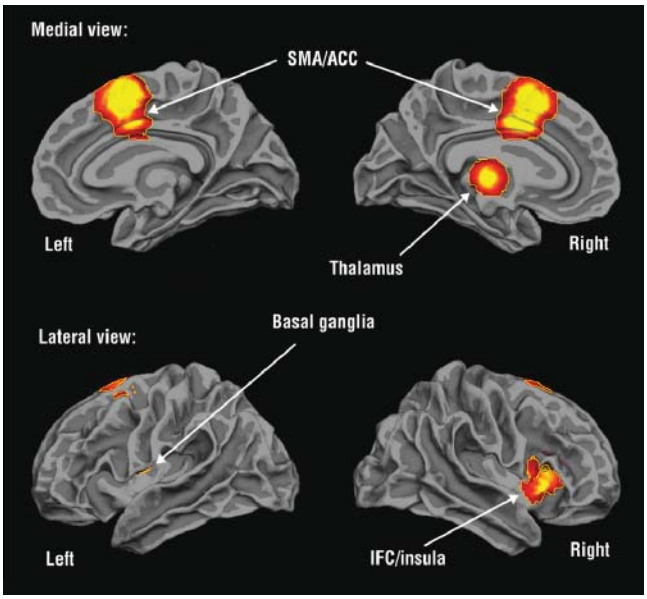


Figure 14.13 Altered brain activation during inhibition tasks in ADHD. Meta-analytic results. IFC = inferior prefrontal cortex; SMA = supplementary motor area (SMA), ACC = anterior cingulate cortex (ACC) Color picture available online See footnote 1. *Source:* Reprinted with permission from H. Hart, J. Radua, T. Nakao, D. Mataix-Cols, & K. Rubia (2013) Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: Exploring task-specific, stimulant medication, and age effects, *Journal of the American Medical Association Psychiatry, 70*(2), 191.

cingulate cortex, and thalamus. As noted earlier, the role of the thalamus in response suppression has been discussed for several years. Only recently, however, have imaging studies begun to highlight the thalamic component of the neural networks involved in type 2 processing in ADHD.

Impulse Control: Interim Conclusions and Additional Considerations

Neither response interruption nor temporal discounting mechanisms claim to provide a complete account of impulse control. Other relevant considerations are that impulsive ideas come from many sources; motor and language development affect level of control; personality attributes (e.g., optimism) modulate impulse regulation and discounting; and other modulating mechanisms could be identified.

Nonetheless, four salient interim conclusions stand out. First, fractionation of the impulsivity domain at the behavioral level in ADHD (e.g., using personality measures) has been largely lacking. This is important because much research relies on the *DSM* symptom domain of hyperactivity-impulsivity, but it includes only three impulsivity items that poorly capture the range of impulsivity in the literature. Second, reactive or anxiety-based response suppression (behavioral inhibition) does not appear to be central to ADHD, apart from its linkage to early-onset conduct disorder. Third, abnormal reward response, particularly related to temporal properties of reward, shows promise as a potential contributing causal mechanism in at least some cases of ADHD and to the hyperactive-impulsive behavioral symptom domain, suggesting that type 1 processes may be involved. Fourth, measures of response suppression or inhibition show consistent and moderate-size effects in children with ADHD, albeit clearest and most well-replicated in only a few measurement paradigms (e.g., stop signal task) that still receive some debate as to their properties. These response suppression measures are reflected in altered neural responding during these tasks, beginning to set the stage for increasingly elaborated cognitive-neuroscience models of ADHD. Clinical applications will require better integration of these models and resolution of measurement questions that remain for the most sophisticated laboratory measures.

Heterogeneity and Multiple Developmental Pathways: Recent Developments

Nosologists face a recurring dilemma—seek unity across apparently distinct conditions, or else seek differentiation within an apparently single condition. In the first approach, investigators may identify a common personality dimension of constraint or behavioral inhibition that cuts across ADHD, ODD, conduct problems, aggression, and substance abuse, helping to unify those disparate disorders under a single rubric (Krueger & Markon, 2006; Tackett et al., 2013). In the second approach, investigators identify more homogenous subgroups within a single disorder. For example, the field has seen progress with the differentiation of conduct disorder into childhood-onset persistent versus adolescent limited (Moffitt et al., 2008) as further refinements of this developmental taxonomy are emerging (Fairchild, van Goozen, Calder, & Goodyer, 2013). Both approaches are necessary in converging on a refined understanding of developmental psychopathology and developmental trajectories. The unifying approach has helped, for example, in clarifying the extent of shared genetic liability for many forms of psychopathology (Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011). The splitting approach, meanwhile, has been helpful in clarifying the etiology of conduct disorder and mental retardation and other diseases like cancer.

When it comes to ADHD, as noted at the outset of this chapter, it is helpful to recognize opportunities for lumping. Thus, it has been useful to recognize the overlap of hyperactivity-impulsivity with emotional dysregulation, with conduct disorders, and with substance abuse disorders. Likewise, it is useful to recognize the overlap of inattention-disorganization with learning problems, as well as with internalizing problems like anxiety.

At the same time, and as emphasized in this section, it can be helpful to recognize and parse the considerable heterogeneity within the ADHD population. This section considers how different fractionations of the ADHD domain can be accomplished that may shed light on distinct and perhaps more homogenous subgroups that may prove to have better validity in terms of neurobiology and clinical prediction than does the current ADHD definition.

Three approaches have been taken to parse ADHD. The first approach relies on clinical observation followed by empirical validation. For example, as noted earlier, a recurrent theme in the literature has been the possible existence of a group of children with inattention without hyperactivity, sometimes referred to as sluggish cognitive tempo. This chapter reviewed a handful of studies suggesting distinct psychological mechanisms in a refined inattentive group. Additional review of this domain is provided by Barkley (2014) and by accompanying articles in the same special issue of *Journal of Abnormal Child Psychology* (Becker, Marshall, & McBurnett, 2014).

A related clinical approach has focused on the subgroup of more aggressive or antisocial youth with ADHD. More recently, we pursued this idea using a refinement borrowed from recent work on conduct disorder, known as the *callous-unemotional* trait. In the conduct disorder realm, it seems that important differences in etiology, prognosis, and treatment response accrue to children who present as callous-unemotional (Frick, Ray, Thornton, & Kahn, 2014). This term designates a tendency to be indifferent to the needs and feelings of others, and to display a lack of empathy. It is reminiscent of adult psychopathy, but is not synonymous with psychopathy because children who are callous-unemotional, although at elevated risk of severe antisocial behavior, do not necessarily go on to be psychopathic as adults (Frick et al., 2014). The term nonetheless carries substantial risk of stigma when applied to children and therefore provokes considerable caution in applied settings. (For this reason, the *DSM-5* used the term with limited prosocial emotions.) In the case of children with conduct disorder, it is most relevant due to the potential of differential treatment response that can improve outcome for these children (Frick & Nigg, 2012; Frick et al., 2014).

Because emotional dysregulation as well as aggression commonly overlap with ADHD, this approach may also be fruitful in ADHD even when conduct disorder is not present, although for now we do not know whether it will be relevant to improved treatment tailoring for children with ADHD and so it is not being suggested that it should come into use in clinical practice for youth with ADHD. Even so, it may help us understand neurobiology in the research setting at this stage. To examine this, we (Musser et al., 2013) measured two cardiac parameters of emotional regulation. The first, the preejection period, is conceptually related to type 1 regulatory processing. The second, respiratory sinus arrhythmia, is an index of vagal tone and is conceptually related to type 2 regulatory processing (Beauchaine, Katkin, Strassberg, & Snarr, 2001). Children with ADHD without conduct disorder watched an emotionally evocative film, while cardiac measures were obtained. They were divided based on their surface phenotype (behaviors) into two groups. The first group was rated by both parents and teachers as beyond the 95th percentile (compared with national norms) in their lack of prosocial behaviors like empathy. They were designated as callous-unemotional and comprised about a third of the ADHD sample.

The results were striking and are reproduced in Figure 14.14. The left panel (A) shows results for the sympathetic or type 1 process. The two ADHD groups are on the opposite side of the typically developing children, with type 1 process of over-arousal characterizing the main group of ADHD children, while under-arousal characterizes the callous-unemotional group of ADHD. Differences are most striking in the presence of negative emotional stimuli, which tend to over-stimulate the ADHD youth but to which the callous-unemotional youth are relatively

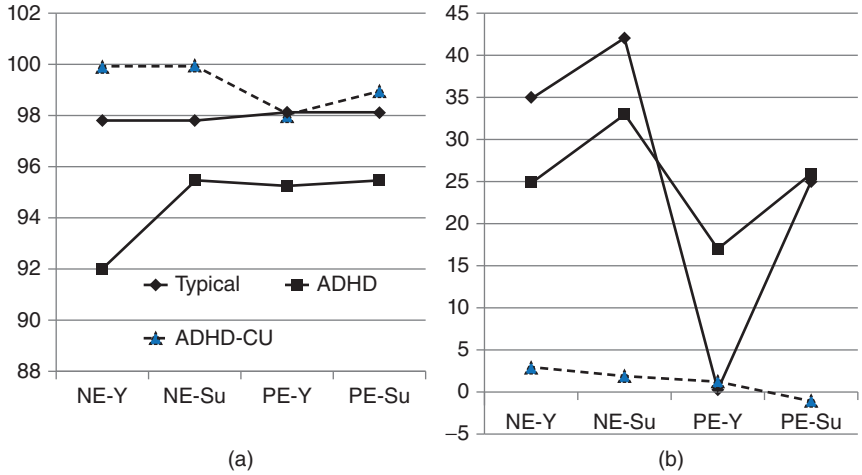


Figure 14.14 ADHD physiology and CU subgroup. Three groups are depicted: typically developing children (typical, $n = 128$), ADHD ($n = 54$), and ADHD with callous-unemotional features (ADHD-CU; $n = 21$). The x axis depicts four emotion conditions: (1) negative and (2) positive emotion (NE, PE); (3) emotional induction (Y); and (4) suppression (Su). Panel A: Preejection period on the y axis; higher value = lower sympathetic arousal. Panel B: Respiratory sinus arrhythmia (*100) difference from baseline (at 0) on y axis; higher value = greater regulatory engagement. *Source:* Adapted with permission from E. D. Musser, H. S. Galloway-Long, P. J. Frick, & J. Nigg (2013) Emotion regulation and heterogeneity in attention-deficit/hyperactivity disorder, *Journal of the American Academy Child and Adolescent Psychiatry, 52*(2), 169.

indifferent in terms of autonomic response. The right panel (B) shows results for respiratory sinus arrhythmia or type 2 process. Here the callous group showed a failure to engage regulatory processes at all, indicating they did not perceive an emotional challenge to be regulated. The ADHD group had a normal, but muted, regulatory response. What is helpful about data of this nature is that they reveal physiological differences within the ADHD population that are hidden when simply looking at all children with ADHD together, and, crucially, that do not appear when considering the *DSM-5* presentations.

A second fundamental approach is to use clustering techniques to regroup children with ADHD based on their configuration of ADHD symptoms. This approach has been used in several studies and is reviewed by Willcutt et al. (2012). In brief, it tends to replicate a set of several ADHD types that maps only partially onto the *DSM-5* presentations. Most striking is that these studies tend to support the existence of the hypothesized group with ADHD without hyperactivity, and suggest that the best cut point symptom-wise for that group is 2 or fewer symptoms of hyperactivity and 5 (or 6) or more symptoms of inattention. As reported earlier, Carr et al. (2010), Goth Owens et al. (2011), and Derefinko et al. (2008) used similar cut points to show somewhat distinct cognitive response patterns in that subgroup with ADHD.

A third approach also uses clustering algorithms, but instead of relying on ADHD symptoms tries to look at measures of mechanism that might be more closely related to neurobiology. To again borrow an example from our group, Fair et al. (2012) used a clustering technique to find subpopulations of children with ADHD with distinct profiles of neuropsychological measures. We identified four subpopulations that are depicted in Figure 14.15. It suggests that one ADHD group is impaired on type 2 processes represented by cognitive control, with poor performance on response inhibition, working memory, and memory span. A second group is impaired on a capacity process, here indexed by reaction time variability. A third group is impaired only on time estimation, an ability that depends on cerebellar-frontal connections. A fourth group also has a capacity problem, with deficits in signal detection. While more investigation will be needed to determine how the two capacity oriented groups differ, overall the model suggests that some forms of ADHD are characterized by breakdowns in type 2 processing, others in type 1 processing or resource capacity. More work will be needed to replicate this study, to integrate it with measures of reward discounting, and to determine whether the hypothesized brain differences proposed here in fact

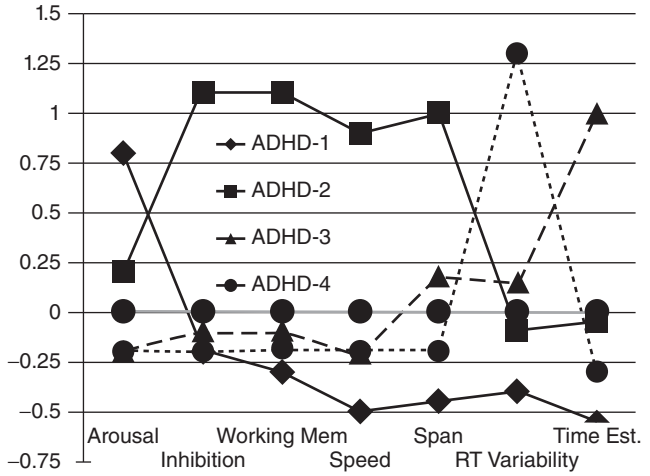


Figure 14.15 ADHD neuropsychological subtypes suggested by empirical clustering. Derived from graph theory analysis. Control group scaled to 0, all measures are in standard deviation units scaled on control group mean; high scores=poor performance. *Source:* Data from D. A. Fair, J. T. Nigg, S. Iyer, D. Bathula, K. L. Mills, N. U. Dosenbach, … M. P. Milham (2012) Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data, *Frontiers in Systems in Neuroscience, 6*, 80.

emerge. For now this result suggests an approach that may be fruitful going forward.

Further progress was made extending this work forward by our team using measures of emotional regulation derived from temperament theory (Karalunas et al., 2014). We again used a clustering technique to divide up the ADHD population based on parent-rated measures of temperament from the Temperament in Middle Childhood Rating Scale, a version of Rothbart and colleagues' childhood behavior questionnaire (Rothbart, Ahadi, Hershey, & Fisher, 2001) designed for middle childhood. These parent ratings have several advantages: (1) they are similar to clinical ratings of symptoms, so they are easily extended into the clinic; (2) they overlap the clinical symptom domain while broadening it beyond ADHD; and (3) the dimensions (negative and positive emotion, emotion regulation) have ready linkages to neurobiological systems that are defined in animal work (Nigg, 2006b). These results were also quite heuristic, and are depicted in Figure 14.16. (The figure displays 7 of the 16 temperament scales used, for simplicity.) One group was labeled as *mild* ADHD because their emotional regulation was essentially the same as the normal control group. The second group was labeled as *surgent* because they were high in activity and positive emotion. The third group was labeled as *irritable* because they were high in anger and low in soothability, connoting

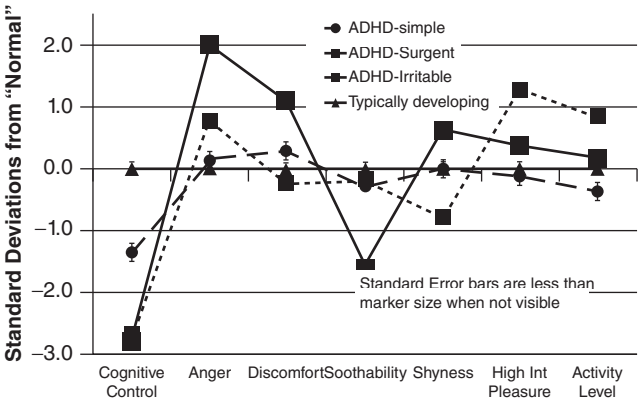


Figure 14.16 ADHD temperament types suggested by empirical clustering. Three temperament based subtypes of ADHD based on a graph theory analysis of maternal ratings. $N = 310$ ADHD, 180 typically developing. Control children scores are scaled to 0 on all scales; the y axis is standard deviation units scaled to the control group.

a tendency to extended anger outbursts and tantrums (Shaw et al., 2014). These children might be expected to exhibit negative urgency impulsivity as discussed earlier. While these groups are clinically recognizable, what was significant about this was study was the external validations conducted. Clustering techniques are no more than exploratory results or hypotheses, because any set of data can be clustered in an almost infinite number of ways. We therefore validated extensively.

First, we showed that the pattern reproduced in a random split of the sample, indicating results were not simply random. To confirm that, we perturbed the data using a variation of information algorithm. The results were robust to data perturbation, meaning that changing some data points to random data did not readily change the story. We next showed that when the same children were seen one year later and the clustering techinque repeated, the same three clusters appeared. Moreover, most of the children in the surgent and negative emotion groups remained in those groups. The mild ADHD group, however, was less stable.

Having done extensive internal validation, we then examined three kinds of external validators. First was the cardiac indicators mentioned in the callous-unemotional study by Musser et al. (2013). Here, we found that the surgent group had a dramaticaly different and unusual regulatory profile, tending to apparently release rather than exert regulation in the face of emotional stimuli, especially emotionally positive stimuli. Striking also was that the mild group had a normal physiological pattern. Second, on functional brain imaging, all three groups differed from each other and from the control group (although we only had imaging data on a small subset of the sample so that particular finding is somewhat preliminary). However, the irritable group had the most striking unique pattern, exhibiting underconnectivity from amygdala to insula, suggesting a breakdown in neural circuits that regulate negative emotions. Third, we examined clinical outcomes one year later. The negative emotion group had a 50% chance of incurring a new psychiatric diagnosis in the ensuing year, versus less than 20% for the other groups. The ability to predict this clinical outcome by this grouping was unmatched by other clincial methods including *DSM* presentations, comorbid picture, or callous-unemotional tratis. This configuration of types or subphenotypes therefore emerges as a superior clinical predictor to any existing symptom picture that might be obtained with children with ADHD. It suggests these subphenotypes as new targets for etiology research.

This last finding about clinical prediction points to the fourth, and perhaps most powerful (and as yet hardly attempted) approach to ADHD subclassification: longitudinal course. While it is know that children with ADHD differ in longitudinal course, little systematic work has formally mapped these trends statistically for predictive purposes. To illustrate this from a related field, we (Jester et al., 2008), conducted a longitudinal study of changes in attention and conduct problems from age 5–17 years as measured by teacher ratings, and related these to early onset drug and alcohol use (a major predictor of substance abuse problems later). We found that drug use was predicted in novel and important ways by the developmental trajectory of attention problems as opposed to the cross sectional number of those problems. At a neurobiological level, the NIMH intramural group several years ago initiated a longitudinal study of structural brain imaging (structural MRI looking at gray matter volumes). This work bore fruit since the last edition of the current book. It suggests that ADHD outcomes are related to trajectory of brain development and highlight the importance of cortical thickness as an endophenotype measure (Shaw, Lerch, et al., 2006; Shaw et al., 2013).

Summary of Heterogeneity

Both lumping and splitting approaches are important to clarify nosology. In the case of ADHD, it is likely that in addition to being related to other disorders, the current definition also encmopasses more than one biological group that is not mapped onto existing descriptive types or presentations. The several methods available suggest that work

toward an improved nosology is becoming tractable. Such work benefits from appeal to neurobiologically based measures of type 1 and type 2 regulation.

FUTURE DIRECTIONS AND CONCLUSIONS

The future is exciting for studies of ADHD, and my hope is that this chapter conveys some of the progress, possibilities, and excitement that characterize the field at present to both young and seasoned investigators. I consider key future directions, including some areas not covered in this review, and then conclusions.

With regard to the future, one theme of this review has been that the field continues to accumulate evidence not only of neurobiological correlates, but now of neurobiological heterogeneity in ADHD. This heterogeneity is on the cusp of being tractable. As this goes foreward, we may confirm that ADHD does contain within it subgroups that have distinct neurobiology with a stronger clinical signal than is available from existing clinical types. It therefore appears that, in time, the field should be able to improve on the current nosology for ADHD. The method of doing so, suggested by us and also by Lenzenweger (Lenzenweger, McLachlan, & Rubin, 2007) is illustrated in Karalunas et al. (2014) in the prior section.

This means that a core future direction is the further confirmation and further development of refined subphenotypes as targets for biological analysis. Clinical types, apparent from observational measures, need to go beyond ADHD symptom dimensions and examine core dimensions related to neurobiology, including clever use of measures of the subdomains of type 1 and type 2 attention and impulse regulation described herein but also, crucially, the domains usually thought of as involving emotion regulation (such as irritability, anger, and dysphoria), which are inseparable from ADHD due to the intricate interrelatedness of self-control, self-regulation, attention, arousal state, and emotion.

With that work going forward, what might it achieve? What might a future nosology look like? It is too early to tell, but by drawing upon some principles of this review one can speculate the following with regard to the nosology of clinical presentation. First, it will be helpful to differentiate children in regard to whether the primary problem is in (1) type 2 processing or in (2) type 1 processing or resource capacity. Second, it will be important to recognize that breakdowns in emotion regulation and in cognition need to both be considered in subdividing this population for clinical purposes and for etiological study.

Children with problems in type 2 processes may resemble the group seen by Fair et al. (2012) that has global problems in executive functioning, yet may not have marked problems in emotional regulation, corresponding to the mild group seen by Karalunas et al. (2014). Children with type 1 processing problems may be extremely impulsive, like both of the emotionally dysregulated groups seen by Karalunas et al. (2014). Those who are extremely irritable may have a problem with type 2 regulation of emotion, while those who are callous or exhuberant may have problems with either underarousal or with type 1 regulation of reward signals. Integrating these different possibilities will require extensive exploration, and probably will lead to modifications of this model.

However, in addition to neurobiology and nosology of child features, nosology of *context* is also needed. That work has scarcely begun. Thus, a second key future direction is to better characterize the contextual limitations and influences on neurobiology, and to identify when context is more important than neurobiology for purposes of nosology. For example, this review has had little to say about race, ethnicity, or culture (more discussion of race and culture in relation to ADHD is provided in Nigg & Barkley, 2014). Yet their influence on what is described herein may be far reaching. Aside from active work in Brazil and Oceania, with a small literature out of Israel and out of Puerto Rico, most of the scientific and clinical literature on ADHD has been from the northern hemisphere and from Western Europe or English-speaking parts of North America. This is rapidly changing as work scales up in China, Japan, Iran, Korea, Mexico, Argentina, and elsewhere. Meantime, in Europe and English speaking North America there has been a relative and substantial neglect of the real boundaries of ADHD neurobiology across race and culture (e.g., African-American and Latino-Latina youth in the United States). This raises the real risk of medical and psychological practice being misguided in those populations. Increasing foci on individualized and genetically informed medicine will mandate a remedy to this gap in knowledge. Across the world, emerging work in China, the Middle East, South America, Israel, and South Africa promise to help further clarify the boundaries of clinical practice and etiology, but programs in those nations need further development and cross talk with those established in the West. Meanwhile, work in the United States, Canada, and western Europe needs to more aggressively examine race, culture, and ethnicity, particularly as population mixes are rapidly changing on both continents due to immigration. This work is beginning and needs to markedly expand. It is notable that

environmental risk factors, emphasized herein, vary widely across these settings and this will be a critical source of trying to understand developmental epigenetics of ADHD.

Related to this point (because race and ethnicity are often correlated with economic position), recent work has revived interest in the influence of low SES in driving some proportion of cases of ADHD, likely via a range of risk factors that are concentrated and accumulate in disadvantaged population. Several approaches could be taken here, but one striking point is the potential convergence of some classes of ADHD with work on the role of systemic stress (e.g., allostatic load) in the emergence of psychopathology and problems in self-regulation.

A further contextual consideration was mentioned only in passing herein yet represents another future direction, and that is the rapid changes in children's socialization by social networking, internet, and other online media and how they may influence ADHD (Pea et al., 2012; Smith & Livingston, 2014s). This domain is having poorly understood effects on children's socialization that will require integration with other methodologies as we consider environmental effects.

Third, emanating more directly from the core material in this review, a major next direction for ADHD will be mapping G×E effects in detail. A shift toward mechanism is occurring. Success likely requires better understanding of epigenetic effects (via DNA methylation, histone methylation, chromatin remodeling, or other mechanisms). Progress will be slow at first, and will eventually join up with related work in other areas of psychiatry. Epigenetic studies require careful balancing of the limits of studies of peripheral tissue in disorders thought to originate in the brain, while also recognizing the profound potential for identifying new diagnostic biomarkers that are more powerful than genomic structure (DNA allele or genotype). For example, recent work illustrates in animals that lead exposure a known correlate of ADHD in humans; (Nigg, 2008) leads to overactivity in rats and this is mediated by altered histone methylation in the hippocampus (Luo et al., 2014; Nigg, Nikolas, Knottnerus, et al., 2010). We recently conducted the first methylome wide study of DNA methylation in children with ADHD, finding in a preliminary sense several signals of methylation related to brain development that may hold promise for future exploration (Wilmot et al., 2014). One can imagine that at some point in the not-too-distant future, we may be able to create active cross talk between animal studies and methylation markers identified in children with ADHD. At that point we can begin not only to conduct diagnostic tests for biological types based on blood markers but also to type based on the combination of genotype and developmental history. The full realization of this picture is still far off, but work on this vision is a major future direction for the field in ADHD given its status as the most common neurodevelopmental disorder in the nosology.

Epigenetic marks, however, are only the tip of the emerging iceberg for potential biomarker studies in ADHD and other neurodevelopmental conditions. The eventual picture will have to include analysis of high-dimensional data sets that integrate understanding from a systems biology perspective, including RNA expression, protein expression, and metabolite studies (Mason, Porter, & Smith, 2014). These approaches may benefit from newly emerging technologies, such as single molecule sequencing, as well as from the rapidly diminishing costs of genomic and molecular sequencing technologies. However, analytic algorithms to exploit these data still require considerable development for application to the complex phenotypes of neurodevelopmental disorder. Thus progress in this domain is likely to proceed in fits and starts for some time to come as methods come on line, are tried, and are refined.

Further, epigenetic studies raise the possibility of unifying work on early developmental risk factors such as environmental neurotoxicants and ADHD (Nigg, Nikolas, Knottnerus, et al., 2010) with genetics and other ADHD work, helping to resolve a kind of paradox in which one field works on environment and another on genes, without sufficient cross talk. Making this connection can open up more focused targets for prevention in vulnerable individuals. Additionally, epigenetic marks are potentially reversible even in post-mitotic tissue such as the brain (Szyf, 2010). While work on reversing behaviorally relevant methylation or demethylation is in its infancy, the potential for powerful new therapeutic agents is inescapable.

Fourth, as shown in the work reviewed here and by others, ADHD is heterogeneous with regard to outcome. A crucial future direction is to understand this. In part, this means identifying determinants of natural recovery or resilience in children with ADHD, especially in adolescence and adulthood (Cherkasova, Sulla, Dalena, Ponde, & Hechtman, 2013). These remain under-explored and potentially extremely important as clues to future directions (Cicchetti, 2013). The contemporary brain imaging literature that was summarized in this chapter is almost entirely confined to cross sectional studies. The only longitudinal studies to date have focused primarily on gray matter volumes or cortical thickness. Thus, a major future direction will be longitudinal studies of functional brain imaging in ADHD, using either resting state or task-based metrics to map functional neurobiology in vivo.

Finally, whereas this chapter outlines in detail the rich possibilities for capturing ADHD phenotype and subphenotype at multiple levels of analysis, genetic studies have as yet not taken much advantage of advances in brain imaging or neuropsychology. In part this is a logistical problem: genetic studies as conducted to date require massive samples (upward of 10,000) to get adequate power to see effects. Genome wide association studies using sample sizes of 25,000 to 40,000 ADHD cases and more are in preparation and will be appearing in genetic studies of ADHD around the time this volume appears in print. Conducting sufficient neuromimaging or even neuropsychological evaluation for such work is still in progress around the world and will take longer. Yet, pooled consortia are beginning to reach this point. The ENIGMA consortium has begun to examine GWAS data in relation to structural brain imaging metrics (Thompson et al., 2014) and this consortium is continuing to expand and improve the brain metrics it can examine via pooled analyses. Even on a smaller scale, however, it is possible to conduct statistically powerful work using gene pathways or prioritized gene sets in relation to novel and more contemporary brain network metrics (Mooney, Nigg, McWeeney, & Wilmot, 2014). Doing so should have the purpose not simply of correlating genes and brains, but of identifying biological subtypes of ADHD that can be cross-replicated in brain and gene (as illustrated in part by Karalunas et al., 2014).

It is worth pausing on this last point. It can be seen from the prior examples that different causal mechanisms may lead to the same ADHD phenotype or that distinct mechanisms may be associated with novel subgroups of ADHD that all have the disorder. These types of findings exemplify equifinality but also enrich our thinking about which children truly have a clinical disorder. Do children with a simple under-controlled presentation, but with normal sympathetic and parasympathetic physiology and benign clinical outcomes, have a clinical disorder? We can also imagine moving closer to personalized medicine: do children with an irritable presentation benefit from a distinct pharmacology or behavioral intervention at higher rates than other children with ADHD?

Many challenges suggest that realizing such hopes remains some distance off. For example, tracing the course of development and recognizing which developmental path a given child is on will take more work. To give an analogy, pediatricians routinely examine growth charts to locate the growth trajectory of a child patient. In subsequent years, they do not ask whether the child is tall or short for age, but rather whether she has diverged from the prior trajectory. In the same way, we can imagine mapping trajectories of change for ADHD that reflect routes for temperament types, neurocognitive types, or even brain profiles, and then asking in future assessments whether they remain on an improved, same, or worse trajectory compared with the prior picture.

A key challenge will be in actual clinical implementation. Current clinical practice remains accustomed to diagnostics reliant on simple algorithms and symptom lists. Combining of future data will likely require the field to abandon simple diagnostic algorithms that clinicians keep in their head (as is now done in *DSM-5*) and instead move to complex algorithms that use machine computations to assist with diagnosis. Clinicians of the future may rely instead on complex algorithms implemented in handheld computing devices, which become a vital tool of psychiatric and psychological assessment.

A final key research consideration will be extending these trajectories back to very early life. Nearly all clinical prediction work in ADHD, be it treatment outcome or brain imaging, goes no younger than 3–4 years of age. Yet it is quite likely that indicators of ADHD may be seen in early infancy or even before birth, if we know where to look (Auerbach et al., 2004; Sullivan et al., 2015). Such work on the early developmental origins of ADHD, of self-regulation, and of the early programming of response tendencies represents a major opportunity for the next generation of research. This approach is particularly compelling when we consider epigenetics, because the prenatal and early postnatal periods are likely to be of primary importance for epigenetic change and programming. The long term hope of preventing ADHD, so as to allow vulnerable youngsters to achieve their full potential without developmental handicap, will ultimately require understanding these early origins of the emergence of self-regulation.

Overall, progress in the last decade has shown several trends for this field. First, a gene × environment perspective is increasingly ascendant and lays the groundwork for imagining epigenetic models of neurodevelopmental conditions like ADHD. Identification of epigenetic mechanisms could, conceivably, bring a turning point in the coming century, but how soon this can be done for human behavior will depend on improved technologies that have yet to be invented, which would enable assessment of epigenetic change in the central nervous system in living humans. This in turn has revised interest in specifying the developmental environments associated with ADHD in conjunction with genetic analysis. Second, multiplicity of types and mechanisms within the ADHD population appear to exist and are increasingly recognized. Reaching some consensus on how they can be best characterized is

now a chief goal in the field as we begin to imagine moving toward personalized care for children within the ADHD rubric. Third, integrated multilevel analyses of ADHD, that take into account genes, environments, physiology, and brain function are increasingly becoming normative around the world. Seeing whether these rich assessments actually can enhance clinical outcomes will be the critical test of utility for this type of work in the coming generation.

In conclusion, self-control and self-regulation are of ubiquitous interest in regard to human adaptation and mental health. ADHD is a paradigmatic disorder that encompasses and exemplifies many of the developmental processes involved and how they may go awry. Use of a two-process perspective is useful in beginning to understand and unpack the complexity in this syndrome. Study in this area is in an exciting phase and opportunities abound for dramatic progress in the decades to come.

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CHAPTER 15

The Development and Ecology of Antisocial Behavior: Linking Etiology, Prevention, and Treatment

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A BRIEF HISTORY

Children and adolescents who are uncooperative and angry and who steal, fight, destroy property, break the law, and attack others have always been a concern for adults. Antisocial behavior in youths is costly and unpleasant to parents, peers, and the community. Moreover, chronic antisocial behavior in childhood and adolescence is the major disruptor of healthy development and results in pain and suffering in adult relationships, patterns of incarceration, disturbed mental health, and difficulties in employment (Miller, 2004).

Research into antisocial behavior has long been an applied science, largely in response to these disruptions to youthful lives and the community. Experts who have studied and written about the nature of delinquent behavior are also those who are concerned with the design of rehabilitation services. Healy (1926) initially observed that delinquent youths were in frequent company with delinquent peers but hesitated to attribute causal status to peers. Inspired by the new psychodynamic perspective of the times, some researchers surmised that antisocial behavior in children was motivated primarily by internal conflicts and turmoil, mostly from troubled relationships with caregivers. Speculation about the influence of peers, however, shifted a bit when the effectiveness of various rehabilitative services for delinquent youths was evaluated (Healy & Bronner, 1936). In the context of a quasi-experimental design, Healy found less recidivism among youths in foster care treatment in Boston than among youths grouped in institutional care in Chicago. These findings suggested that warehousing youths with other troubled youths might actually exacerbate their problems. Although this was not a randomized trial, the finding portended future findings about the problems of peer influence in group care (Dodge, Dishion, & Lansford, 2006; Leve & Chamberlain, 2005).

Criminology

The field of criminology emerged from a confluence of psychological and sociological theories and methods. Accordant with the logical positivist philosophy of science (e.g., Popper, 1959), a plethora of longitudinal studies was conducted to determine which children become delinquent. The methods of these early longitudinal studies were intensive and often involved extensive home observations and carefully transcribed caseworker notes (e.g., Glueck & Glueck, 1950). These studies often took many

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decades to code, tabulate, and analyze before their full scientific value was realized (Elder et al, 1986). For example, the findings from a longitudinal study with an embedded randomized prevention trial conducted prior to World War II did not yield findings until 30 years later (e.g., McCord, 1978). Fortunately the findings were well worth the wait. For example, the Cambridge–Sommerville youth study found that early harsh parenting (coded from home visitor ratings) was prognostic of later antisocial behavior and aggression. For the prevention trial, early-adolescence youths were carefully matched and then randomized to a 4- to 5-year intervention experiment that ended at about the time the United States entered the war. After 30 years of follow-up, much to the surprise of the scientific community, the youths in the intervention group had somewhat worse outcomes than did those in the control group. Four to five years of social work apparently had no effect or perhaps even had an iatrogenic effect.

Several patterns of findings emerged from the early criminological studies about predictors of delinquency, which investigators reviewed in the early 1980s. Meta-analysis of all the existing criminological longitudinal studies on the prediction of delinquency revealed that disorganized, harsh, and lenient family environments were the most prognostic of future delinquency (Loeber & Dishion, 1983). A close second in predictive power was the youths' own problem behavior in childhood, with teacher ratings being most prognostic, followed by parent ratings. The patterns of findings across the early criminological investigations were largely replicated in more recent longitudinal work on the prediction of crime, such as the Cambridge Youth Study (Farrington, 1985; West & Farrington, 1973). In general, paradoxical patterns of harsh and overly lenient parenting result in children arriving to school with problem behaviors, which in turn is prognostic of escalation to more serious forms of delinquent offending in adolescence and beyond. Not surprisingly, early onset of problem behavior was found to be associated with escalations to more serious and repeated offending in adulthood (Farrrington & Gallagher, 1986; Robins & Hill, 1963). Measures of children's cognitive abilities and genetic vulnerability were only modestly predictive of future delinquency (Loeber & Dishion, 1983).

Many of the early longitudinal studies on the etiology and prediction of delinquency did not measure peer environments. It was not until the 1950s that criminologists, such as James Short, began to speculate about the causal role of peers in the development and escalation of antisocial behavior (Short, 1957). Differential association theory motivated the study of group processes associated with gangs, in particular the Chicago "street corner" gang (Short & Strodbeck, 1965). These early studies of peer dynamics amplifying delinquent behavior were largely observational. However, at the same time, learning theory was dominating the study of behavior. The match between differential association theory and learning theory was natural and adopted by criminologists as an explanation for crime and delinquency (Burgess & Akers, 1966). Direct observations of group institutional settings verified that the rich reinforcement for deviant behavior provided by peers far outweighed the meager rewards for prosocial behavior provided by adults in the same setting (Buehler, Patterson, & Furniss, 1966). Further support for the unique contribution of peers to the development of delinquent behavior in criminology was found in larger community studies (Elliott, Ageton, & Canter, 1979; Jensen, 1972). Most theories of crime thereafter have conferred causal status on peer influence in general (Reiss, 1988), and on gangs in particular (Thornberry, 1998).

Child Psychiatry and Psychology

Until the late 1970s, child psychiatry and psychology were neophytes to the scientific study of antisocial behavior in children. Psychology brought two major contributions to the scientific study and understanding of antisocial behavior. The first was a developmental perspective, initially formulated as developmental lines (Freud, 1963). Psychiatric epidemiology was an emerging science with unique design features and methodologies. For example, the case control method of identifying youths at risk and conducting follow-up assessments with them and with the case controls became part of the scientific literature. For example, in the Robins and Hill (1963) study, it was suggested that the developmental patterns of early-onset and late-onset antisocial behavior had unique etiologies. The early- and late-onset developmental pathways to adult antisocial behavior later became an organizing principle in theories about the etiology of antisocial behavior (Moffit, 1993; Patterson, 1993).

Psychology's strong emphasis on measurement theory made a major contribution to the study of antisocial behavior. Advances in the science of psychological measurement were made largely as a function of the massive demands on psychologists to assist with the selection and deployment of young adults to World War II (Wiggins, 1973). The formal guidelines for testing individual differences in basic concepts as *traits* were developed, and the concept of a *construct* was born (Cronbach & Meehl, 1955). A methodological framework was articulated for statistically differentiating between variation in a measurement method and a personality trait construct (Campbell & Fiske, 1959). For example, one could explore whether

teacher and parent ratings of a child's antisocial behavior reflected a trait of the child or unique reporting biases of each adult. It turns out that indeed, when multiple measurement methods are used there is ample evidence that children's antisocial behavior reflects a trait of the child (Patterson, Reid, & Dishion, 1992).

Despite the scientific advancements in personality psychology, measurement, and developmental psychology, clinical psychology lagged with respect to scientific rigor. In the early formulations of clinical psychology, treatment was not its strongest suit, and there was very little flow of information between the field of criminology and the psychological treatment of antisocial behavior. In the beginning, treatments for antisocial behavior were exercises in armchair psychology, and theoretical models were applied loosely to the design of outpatient and residential treatment programs (e.g., Redl & Wineman, 1951, 1952). The prevailing view at the time, which is largely shared to this day, was that antisocial youths were best treated by pulling them out of the pathogenic family and peer environment and providing them with intensive residential treatment. Implied is that the more intensive treatment yields the most long-term effects on reducing future antisocial behavior.

Not surprisingly, after scientific scrutiny of intensive residential treatment, pessimism was in order. Although it was possible to create a residential environment in which youth problem behavior was dramatically reduced, therapeutic gains were lost when children were returned to their home and neighborhood environments (Redl & Wineman, 1952).

The experimental approach to studying and analyzing operant behavior formed the foundation of the behavioral revolution in psychological science (Skinner, 1938, 1955). Applied behavior analysis expertise was invaluable for improving the lives of children and adolescents with a variety of psychopathologies. The framework was applied to the design of group homes for delinquent youths in the form of the teaching-family model (Wolf et al., 1976). The model is both humane and sophisticated, with the laudable goal of deinstitutionalizing the treatment of antisocial youths. Unfortunately, careful evaluations of group homes that were using the teaching-family model revealed that they did not reduce antisocial behavior over and above other community group homes. However, compared with community treatment, the teaching-family model was superior for improving academic achievement (Weinrott, Jones, & Howard, 1982). It appeared, once again, that the gains that youths made in the carefully engineered group home facility did not generalize well when they were returned to the community.

A group of investigators began designing behaviorally oriented interventions for the family environment. Several clinical researchers applied operant theory to treat children's problem behavior, with considerable promise of success. First and foremost were Wesley Becker, Rex Forehand, Gerald Patterson, and Robert Wahler (O'Dell, 1974). Patterson's work was noteworthy in terms of the application of conditional probability analysis to understand the antecedents and consequences of specific antisocial acts, which led to the understanding that being mindful of the social interaction context in families provided clues to treatment and prevention (Patterson & Cobb, 1971, 1973). These early studies were process focused. It was particularly intriguing that after weeks of observation, a simple bug in the ear to the mother to change her "antecedent behaviors" led to dramatic reductions in children's aggressive behavior on a case-by-case level (Patterson & Moore, 1979). Studies such as these were critical for the early stages of theory development that integrated an understanding of social interaction dynamics of antisocial behavior with children's developmental trajectories and effective prevention and treatment (Patterson, 1982; Patterson & Reid, 1984; Patterson et al., 1992).

BUILDING MODELS OF ANTISOCIAL BEHAVIOR

Translational Framework

In the 1980s a new generation of longitudinal studies on the development of antisocial behavior emerged. Consistent with a developmental psychopathology framework (Cicchetti, 1990; Cicchetti & Toth, 2009), the studies were conducted with an eye toward designing more effective interventions. The concept of performance models became appealing to the scientific community and to the National Institutes of Health, and longitudinal studies were funded that included direct observations of family interactions that had been previously demonstrated to be sensitive to change in treatment (Patterson & Moore, 1979). The new scientific game was to account for variance in child and adolescent antisocial behavior. If directly observed family interaction accounted for unique and substantial variation in present and future antisocial behavior, those constructs would be promising as targets for prevention and treatment. Thus, an explicitly translational framework was adopted, which resulted in substantial improvements to prevention and treatment strategies.

At around the same time innovations in statistical procedures empowered causal modeling (Jöreskog & Sorbom, 1976). An explosion of longitudinal studies incorporated multiple indicator causal models of a variety of behavioral

issues and a method for directly comparing the fit of competing models (Bentler & Bonnett, 1980). The use of structural equation models provided an explicit means for the simultaneous analysis of both measurement and causal effects in longitudinal models. A seldom-cited breakthrough book by James Dwyer (1983) helped forge the link between measurement theory and causal modeling, showing that classic issues such as multi-trait and -method models could be operationalized and tested within the structural equation environment. Several researchers began to emphasize the value and importance of integrating multiple measurement methods in the analysis of various forms of problem behavior (Dishion & Loeber, 1985; Patterson & Bank, 1986; Patterson & Dishion, 1985). These mostly correlational models of family and peer factors associated with child and antisocial behavior were suggesting that both relationship environments were contributing substantial variance to the development of antisocial behavior. These early correlational pilot studies hypothesized causality but were hardly rigorous tests of mediation and moderation (e.g., MacKinnon & Fairchild, 2009).

Ecology

Urie Bronfenbrenner's (1989) conceptual framework for an ecological perspective on child development became particularly useful for systematic causal modeling. As discussed by Dwyer and several other methodologists interested in structural equation modeling, one of the key shortcomings of a statistical approach was the misspecification problem. Models in which key putative causal constructs are omitted are simply misspecified and the magnitudes of effects biased. Thus it became a central concern of researchers studying antisocial behavior to have a stronger argument for the environmentally and biologically oriented constructs included in a causal model (Dishion & Patterson, 1999). Thus, in two Dishion and Patterson reviews on the development of antisocial behavior, the literature was organized relative to the Bronfrenbrenner framework (Dishion, French, & Patterson, 1995; Dishion & Pattterson, 2006). These reviews reflected an emerging literature about the etiology and course of antisocial behavior that clearly indicated parenting, peer, and self-regulatory mediation and moderation in childhood and adolescence progressions of antisocial behavior. From this literature it was safe to conclude the most contextual stressors on children associated with higher antisocial behavior and crime rates, such as neighborhood and poverty, were mediated by the disruption of parenting and through effects on the self-organization of deviant peer clusters.

Without question, genetic-based vulnerabilities and resilience factors moderate the effect of environments on the development of antisocial behavior. It is likely, however, that behavior–genetic approaches to estimating sizes of shared environmental effects and of genetic effects are not accurate reflections of nature or nurture (Beauchaine & Hinshaw, 2008). One key factor to consider from a modeling perspective is the measurement method: parent reports tend to produce somewhat higher estimates of genetic effects than do direct observations of behavior (Bullock, Deater-Deckard, & Leve, 2006; Leve, Winebarger, Fagot, Reid, & Goldsmith, 1998). Regardless, there is considerable value in using twin designs to model estimates of genetic effects, with a particular effort to consider mediation and moderation (e.g., Lemery-Chalfant, 2010; Meier, Slutske, Heath, & Martin, 2011). Recent efforts to integrate adoption designs are noteworthy and suggest the cross-fostering conditions of key causal processes, such as family conflict. For example, Harold and colleagues used a twin and an adoptive design to examine the role of interparental conflict and found substantial evidence that the effects on early emergence of antisocial behavior were not simply passive correlations of shared genetic traits (Harold et al., 2013). The integration of multiple design frameworks is the future for research on the ecological conditions giving rise to antisocial behavior, as well as drug abuse, high-risk sexual behavior, and violence.

During the past 10 years research has moved rapidly toward direct measurement of genetic polymorphisms associated with development of a variety of human behavioral characteristics, including antisocial behavior (Rutter, 2006). Caspi and colleagues, for example, tested a model with a gene by environment interaction that accounted for adult violence in males. In this model, boys with the MAO-A single nucleotide polymorphism who also had been exposed to parental maltreatment in early childhood were the most likely to be violent adult offenders (Caspi et al., 2002). Cicchetti and colleagues, who also examined the impact of child maltreatment on the development of antisocial behavior, significantly extended this finding. Among youths with a history of maltreatment, three genetic polymorphisms (tryptophan hydroxylase, serotonin transporter, and MOA), amplified the impact of maltreatment on various indices of antisocial behavior in adolescence (Cicchetti, Rogosch & Thibodeu, 2012). The gene by environment interaction also seems to amplify the effects of parenting practices in early adolescence. For example, Dick and colleagues found that youths with

the GABRA2 polymorphism were more likely to develop externalizing problems in the context of low levels of parental monitoring (Dick et al., 2009). Thus, genetic vulnerability for antisocial behavior may come into play in that it amplifies somewhat different aspects of parenting effects in early childhood, middle childhood, and adolescence. Little research to date has examined the moderation of peer effects on various forms of antisocial behavior, a topic discussed in more detail later in this chapter.

Most investigators assume that genetic effects are transmitted to the development of antisocial behavior through identifiable traits, such as temperament. Temperamental traits are characteristics of the child that are observable and define basic action and reaction patterns to the environment and ecology. These endophenotypes have been hotly pursued in scientific research that is attempting to link genetic effects to social behaviors (Gottesman & Gould, 2003). As has been discussed previously, various indices of self-regulation in general and of effortful control in particular seem to be very promising as endophenotypes linking genes with antisocial behavior (Dishion & Patterson, 2006). The pioneering work of Rothbart and Posner (2006) is exemplary with respect to linking imaging of brain neurocircuitry to genetic constitution in research on attention and emotion regulation and the construct of effortful attention control. Remaining unclear is mapping of various temperament traits, such as effortful control, emotionality, and impulsivity, with respect to shared and unique features, but it does appear that the genetic regulation of dopamine receptors lies at the core of vulnerability to development of problem behavior (Beauchaine & Hinshaw, 2008).

As discussed by Leve and colleagues (2010), social mediation of genetic effects is likely to provide a deeper understanding of etiology. Although it is promising, we have yet to show that temperament mediates genetic effects on antisocial behavior, a problem originally identified by Rutter's (2006). Presumably, integration of solid environmental, neuroscience, and genetic research will lead to breakthroughs that trace development from gene, brain circuitry, and temperament, to antisocial behavior. Multilevel models such as these will likely enhance our collective capacity to improve the lives of susceptible children and families.

An ecological view of development assumes that biology and social experience are inextricably linked with the form and function of development. Of particular salience in children's development of antisocial behavior are the patterns of interaction within close relationships, such as families, friendships, and later romantic partners. In the past 10 years, however, considerable progress has been made in research on the relationship dynamics relevant to understanding and reducing antisocial behavior in children and families. Relationship dynamics is a pattern of interactions that cannot be accurately captured in a snapshot of children's lives; it requires measurement over specific periods of time. The history of research on development of antisocial behavior suggests that the study of relationship dynamics has been the most promising in terms of accounting for variance in antisocial behavior in childhood and adolescence (Dishion & Patterson, 2006). Interventions that target relationship dynamics tend to be more reliable with respect to improving children's lives (Weisz & Kazdin, 2010).

This review next focuses on progress made during the past 10 years with respect to (a) modeling the relationship dynamics and ecological conditions underlying the development and course of antisocial behavior, and (b) considering the successes and failures of randomized intervention trials designed to test underlying developmental models.

Micro and Macro Relationship Dynamics

While examining a child's ecology, one can parse the social environment into specific microsocial and macrosocial influences (Dishion & Patterson, 2006; Patterson, in press). Microsocial influences involve relatively immediate action and reaction patterns in which antisocial behavior is learned and amplified. In terms of the development of aggression, parent–child, sibling–child, and peer–child interactions are the most frequently studied relationships. These transactions occur in seconds, and the patterns are observable and reliably quantified in an hour of observation of a relationship.

Macrosocial dynamics evolve over longer periods of time and are often labeled and measured as global outcomes. For example, peer rejection, drift to deviant peers, and academic failure are examples of macro relationship dynamics relevant to the development and course of child antisocial behavior. Changes in network dynamics constitute perhaps the most rigorous definitions of relationship dynamics that are macro. For example, engaging with a gang network in a community can confer status, basic resources, and potential sexual partners (see Dishion, Ha, & Véronneau, 2012), which are functional outcomes that often unfold over the course of days, weeks, months, and years. This perspective is helpful when studying the development of antisocial behavior in children, in that one examines the child's movement from the family, to peers and teachers in school, to friendships and eventually to

an intimate partner, adult family relationships, and relationship networks in the community (e.g., military service, gangs, coworkers, extended family).

From an ecological perspective, when antisocial behavior evokes friendships and deviant peer cliques, the behavior pattern has shaped the social context and network of the individual. Thus, macrosocial effects in turn shape microsocial influences. Once a youth becomes a member of a gang, daily rates of reinforcement for deviant talk and behavior increase, and the payoffs for studying and prosocial relationship development diminish. The same synergistic link could be made between becoming isolated over time and the power of rumination and stress to generate depression. The more one becomes depressed and isolated, the more powerful one's own thoughts become in defining a course of action (e.g., Fyodor Dostoyevsky's *Crime and Punishment*).

This sort of macrosocial function is often of interest to evolutionary psychologists, particularly social adaptations that function to promote survival of both individual and collective gene pools (e.g., Belsky, Steinberg, & Draper, 1991; Ellis, Figueredo, Brumbach, & Schlomer, 2009). The evolutionary framework is helpful for suggesting foci that would otherwise be ignored in a purely psychological analysis. Behavior is shaped by consequences, but the consequences can be viewed from different temporal perspectives and in terms of different units of aggregation (Biglan, 2003). Behavior is also shaped by the momentary reactions of the audience and by the biologically driven need for procreation and group affiliation (Dishion & Patterson, 2006; Dishion et al., 2012).

When relationship niches are considered in the context of the life course, attention is given to the functional dynamics within (i.e., microsocial) and to the movement from one relationship to another (i.e., macrosocial). Several investigators have used the cascade metaphor to represent the development of antisocial behavior from early childhood through adolescence (Dodge, Greenberg, & Malone, 2008; Masten et al., 2005; Moilanen, Shaw, & Maxwell, 2010; Patterson et al., 1992). The key point of the cascade model (see Figure 15.1) is that each developmental stage has its adjustment outcomes and collateral effects that can be seen as products of the outcome. In early childhood, relatively normal challenges in emotion regulation and defiance of parents can lead to problems in school readiness, and lead to failure in academics and peer relationships. Even as early as age 5, marginalized children can associate and reinforce problem behavior, during childhood. Continued difficulties in school and growth of problem behavior predict movement into more serious deviant peer groups. Peer clustering for problem behavior

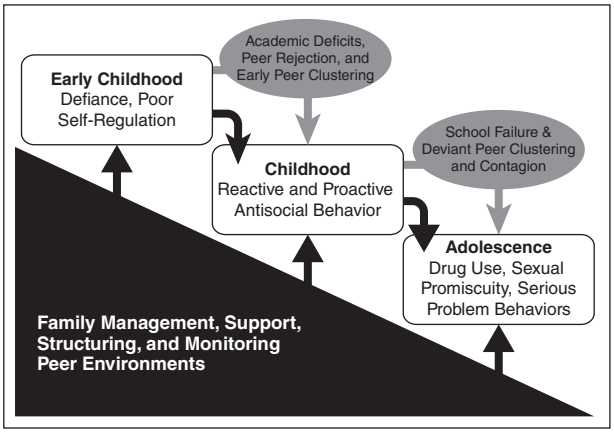


Figure 15.1 A developmental cascade model: parenting contributions and amplifying mechanisms.

is one of the strongest predictors of escalation to more serious antisocial, criminal, and drug use in adolescence. From a biosocial perspective, genetic and other biological characteristics (e.g., sex, puberty) of the child motivate developmental progressions and interact with microsocial and macrosocial dynamics to account for individual differences in various forms of antisocial behavior. We unpack the cascade model shown in Figure 15.1 in the sections that follow.

One of the core achievements in developmental psychopathology is the multilevel analysis of early childhood self-regulation with respect to the emergence of serious forms of antisocial behavior in young adulthood (Cicchetti & Toth, 2009). In this chapter, we focus on two underlying behavioral processes within which thoughts, feelings, and norms are associated with antisocial behavior and its growth over time. Coercion and contagion dynamics at each stage of development can account for variation in numerous forms of problem behavior, beginning with aggression and culminating in multiple forms of problem behavior in adolescence.

COERCION AND CONTAGION DYNAMICS

Coercion is a basic interpersonal dynamic by which individuals use aversive behavior to attain access to rewarding resources and to reduce unpleasant experiences. It can involve being aggressive or unpleasant, or it can play out as emotional manipulation. Although aggression and violence are certainly examples of more extreme forms of coercion, the vast majority of coercive exchanges go unnoticed by the participants. A young child's whining sets the stage for parents to attend to, and potentially reward,

the behavior, for example. However, most parents at some time reverse the pattern and work to teach the child to use language to make requests rather than rely on whining and crying (Patterson, 1982). The coercion process is inherently bidirectional in that it builds on response tendencies of both the child and the parent. The key to change often lies in parents' ability to regulate their emotional reaction to aversive child behavior rather than yell, withdraw, spoil, or hit, and to mindfully manage the child's behavior by using patience and by optimizing opportunities for their child to learn social skills. The link between understanding coercion and promoting family management becomes clear: The latter is the remedy for the former. Positive family management practices reduce the functional utility of coercive dynamics in the family.

Intensive research on the coercion dynamic began in the homes of children referred to outpatient clinics for aggressive behavior (Patterson, 1974). To isolate the underlying patterns that accounted for the coercion dynamic, Patterson and colleagues conducted a series of studies that looked at the conditional probability of a child's aggressive response to a parent's behavior. This series of detailed observational studies revealed the importance of stimulus control in the aggressive exchange (Patterson, 1976; Patterson & Cobb, 1973; Patterson & Moore, 1979). Although work on coercion theory was initially driven by intensive study of clinically aggressive children, the concepts were measured in epidemiologically defined community samples of youths and found to predict escalations in problem behavior from childhood through adolescence (for a review, see Dishion & Patterson, 2006). When the coercion model was then applied to the design of prevention studies, it was found that targeting coercive parenting practices prevented the escalations in problem behaviors one would expect among high-risk adolescents (Dishion, Patterson, & Kavanagh, 1992) and in families undergoing divorce and remarriage (for a review, see Forgatch & Patterson, 2010). These findings suggested that whatever the origins of coercive dynamics in families, interventions that reduce coercion help reduce antisocial and aggressive behavior in childhood and adolescence.

The peer contagion dynamic is of particular interest with regard to the amplification of children's aggression to other forms of problem behavior. Since the beginning of systematic research on antisocial and delinquent behavior, it was observed that peers are core to the problem, but the influence process was unclear (Dishion & Patterson, 2006). Study of the microsocial dynamic called *deviancy training* was begun (Dishion, Capaldi, Spracklen, & Li, 1995; Dishion, Spracklen, Andrews, & Patterson, 1996) by carefully observing the adolescent male friendships of a sample of 13- to 14-year-old boys in the Oregon Youth Study (Patterson et al., 1992). In these videotaped interactions, the boys' deviant talk and their affective reactions were coded in real time. To study the reinforcement of deviant values in verbal exchanges among peers, one must use an extension of the typical learning approach to studying aggressive behavior. Relational frame theory (Hayes & Hayes, 1992) clarified the mechanisms by which reinforcement of words is equivalent to reinforcement of behavior. A uniquely human capability that comes with language is that rewarding deviant talk is as powerful as rewarding the actual behavior.

The matching law was applied to evaluate the extent to which the boys were being selectively reinforced for deviant talk than for other, more normative topics (i.e., relative rate of reinforcement). In general, it was found that the amount of deviant talk in an adolescent friendship was directly proportionate to the friend's relative amount of positive affect in response to deviant versus normative talk (Dishion et al., 1996). Snyder and colleagues (2008) extended the concept of deviancy training to include young children mocking adult behavior, such as pretending to smoke cigarettes during playtime at school. In the studies by Snyder and colleagues, positive affect was also coded and revealed that some youths were mutually reinforcing deviant talk and that this dynamic contributed to later increases in antisocial behavior. The idea that peer contagion has a unique influence on future behavior of children and adolescents has been supported by studies of iatrogenic effects, which have indicated that random assignment to group interventions that aggregate high-risk children can potentially increase problem behavior, and that these increases are associated with deviancy training in the sessions (Dishion, McCord, & Poulin, 1999; Dodge et al., 2006).

Coercion and contagion often occur outside of participants' awareness. Coercion is more characteristic of established relationships in which members share a certain level of fate control, such as parent–child, sibling, and marital relationships. Contagion, on the other hand, is a concept typically applied to understanding how behaviors become disinhibited in the context of age-mates (Dishion & Tipsord, 2011). To study coercion and contagion as real-time behavioral dynamics, it is necessary to code interpersonal events as they unfold over time and to link interpersonal outcomes (ending conflict, mutual laughter) with the coercion and contagion dynamic over time. It is possible, however, to use global ratings of direct observation data to surmise the extent to which a

relationship interaction is characterized by either coercion or deviancy training.

EARLY CHILDHOOD: COERCION IN FAMILIES

Given the evidence that early-onset antisocial behavior is potentially the most problematic for the child and the community, it stands to reason that considerable work would have been done to examine early-childhood parent–child interactions and interventions. This developmental period is characterized by strong dependence on primary caregivers for nurturance, safety, and socialization (Ainsworth, 1989). This foundation is not to be underestimated; lack of it will set the stage for struggles in other periods of development of self-regulation (Rothbart, Ellis, Rueda, & Posner, 2003) and of correlated problem behaviors, such as oppositional behavior and aggression (Olson, Sameroff, Kerr, Lopez, & Wellman, 2005).

Patterson's theoretical framework of coercive family processes is relevant to understanding how the interaction of child characteristics and parenting practices prompts development of early problem behavior (Patterson, 1982; Patterson et al., 1992). Caregiver depression can be a powerful disruptor of positive parent practices when isolated mothers care for young children without adequate support (Wahler, 1980). Depression certainly disrupts positive parenting and the critical exchanges between a young child and his or her caregiver (Hops, Sherman, & Biglan, 1990). However, surprisingly little research has identified the effects of caregiver isolation and depression on actual parent–child coercion dynamics. A notable exception is the work of Shaw and colleagues. In longitudinal research, these investigators found that a tendency for the child to be bold in the face of a fearful stimulus, together with maternal depression at child age 2, were the best predictors of the early-onset trajectory (Shaw, Gilliom, Ingoldsby, & Nagin, 2003).

The study of coercion dynamics presents some difficulty because it requires the measurement of parent–child interaction as it unfolds in real time. With an observed microsocial data stream, one can examine how contingent events lead to escalation of the aversiveness of the interaction. Early on, use of Markov models of social interaction and computation of sequential analyses activated interest among scientists studying microsocial dynamics (Gottman & Roy, 1990), but these models became increasingly suspect, partly because of the base rate problem. Aversive events generally constitute a minority of social events, and the probability of a parent responding aversively contingent on a child's coercive behavior is about .5 of 10% of the interaction. Given the rarity of aversive exchanges, estimates of coercive interaction patterns were somewhat unreliable (Stoolmiller, 2001).

Snyder and colleagues (Snyder, Edwards, McGraw, Kilgore, & Holton, 1994) were the first to consider intensity and duration as critical parameters of escalating patterns of coercion. In an examination of 10 aggressive and 10 nonaggressive preschool children, parent–child interactions were studied for 10 hours. The researchers found that duration of conflict was the key to studying the progression of coercion. Using the Family Process Code, which captures real-time duration of parent–child interactive behavior (Dishion, Gardner, Patterson, Reid, & Thibodeaux, 1983), these researchers determined that parent–child interactions that involved aggressive children were characterized by longer durations of conflict, greater intensity of conflict, and a statistically reliable tendency for the children to be reinforced for their behavior during conflict.

The application of a dynamic systems framework (Granic & Hollenstein, 2003; Granic & Patterson, 2006) is helpful when studying coercive parent–child interactions, and more important, the mutual effects of positive and coercive family interactions. Within a dynamic systems framework, social interaction can be seen as a dyadic state space (Lewis, 1999) in which the microsocial exchange between the parent and child moves from one dyadic space to another (see Figure 15.2). To capture these microsocial dynamics, it is critical to code behavior for all participants in real time and identify duration and emotional valence of all behaviors. As shown in Figure 15.2, the parent (PC) and child (TC) moved from one dyadic state (e.g., mutually positive or neutral, or dyadic positive engagement) to dyadic coercive (e.g., mutual directives, negative talk). These dyadic states are thought to be theoretically meaningful because both members of the dyad are responding in kind. In our work on direct observations of young children from age 2 through 5, we have studied dyadic positive engagement and dyadic coerce, which are summarized in Figure 15.2.

Recently, Smith and colleagues tested the coercion model longitudinally in an ethnically diverse sample of 730 toddlers followed to age 7.5 (Smith, Dishion, Shaw, & Wilson, 2013). Dyadic coercion between the parent and child was measured using duration coding and was found to increase from age 2 through age 5, suggesting that coercion dynamics emerge in early childhood and are not in place at age 2. Key to the coercion model is children's noncompliance (Patterson, 1982). Children's noncompliance was

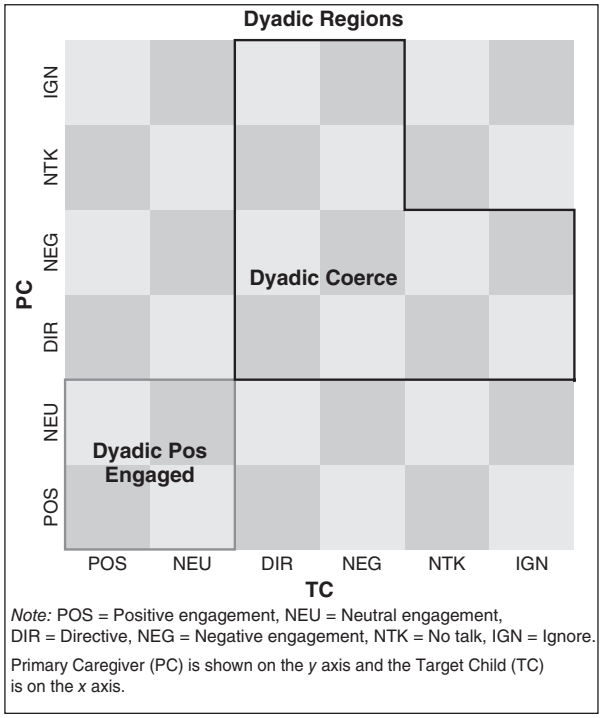


Figure 15.2 A state space grid summarizing parent–child interaction in early childhood. *Source:* Adapted from Hollenstein, T. (2013).

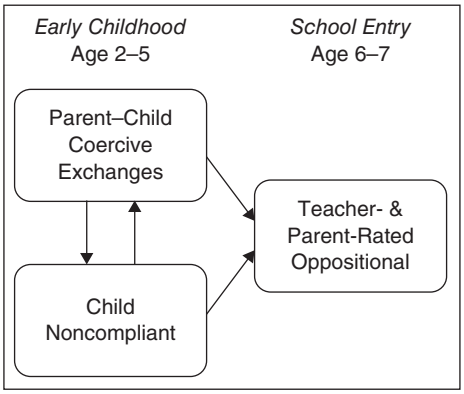


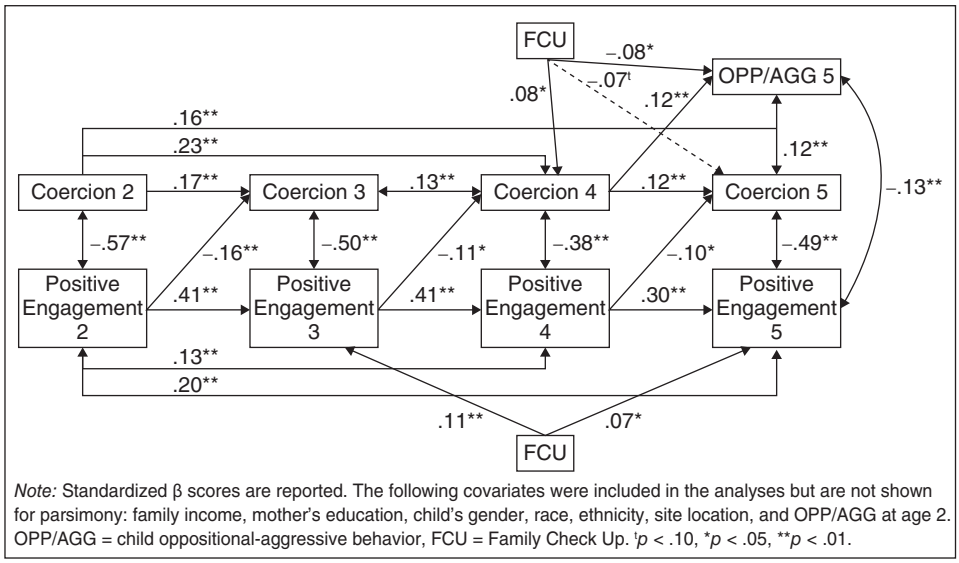
Figure 15.3 Early development of oppositional and aggressive behavior.

rated by coders who watched the videotaped parent–child interaction sessions; mothers rated their child's problem behavior (aggression and oppositional behavior) at age 2, 3, and 5; and teachers rated the child at age 7.5. Findings from the model are summarized in Figure 15.3.

The model summarized in Figure 15.3 was used to systematically test the evocative effects of child noncompliance on parent–child coercion, as well as the reverse. It was hypothesized that these dynamic interaction patterns would be prognostic of growth in oppositional behavior in the home from age 2 to 5 and of teachers' rating of oppositional behavior in first or second grade. It is important to note that teacher perceptions of problem behavior in the first two grades of elementary school are highly predictive of more serious problem behavior in adolescence and adulthood (Loeber & Dishion, 1983; Robins & Hill, 1966). As shown in Figure 15.3, the effects of the unfolding coercion cycle were decidedly bidirectional. It appears that coercion dynamics at age 2 and 3 feed future noncompliance and oppositional behavior problems perceived by parents. However, the reverse is also true: Children's noncompliance and oppositional behavior at age 3 predicts later coercive parent–child interactions. It is especially noteworthy that increases in parents' ratings of oppositional child behavior, the average level of noncompliance during the 4-year period, and coercive parent–child interactions predict teacher ratings of oppositional behavior problems. The model fit the data well, and 22% of the variance in teacher ratings was accounted for by the developmental dynamics underlying family coercion in early childhood.

Of interest to developmental and prevention scientists is the extent to which parent–child positive interactions from age 2 through 5 reduced growth in family coercion. Coercive interactions, albeit risky, occur only a small percentage of the time (estimated 5%). The vast majority of parent–child interactions are either neutral or positive. It is within these positive and neutral exchanges with caregivers that the majority of the socialization takes place. Sitnick and colleagues used a cross-lagged, autoregressive model to examine the mutual effects of dyadic positive engagement and dyad coercive interactions at age 2, 3, 4, and 5, as shown in Figure 15.4 (Sitnick et al., under review). These patterns of mutual positive and coercive interactions were related longitudinally to the child's problem behavior at age 5, controlling for previous levels. As shown in Figure 15.4, it was found that positive parent–child engagement tended to reduce levels of coercive family interaction over time. However, consistent with the Smith et al. (2013) findings, the coercive interaction dynamic was most prognostic of children's problem behavior at age 5. It is noteworthy that randomization to the Family Check-Up, a brief parenting intervention that emphasizes periodic contact with children and families (Dishion & Stormshak, 2007), resulted in improved levels of positive engagement at age 3 and reduced levels of coercive interaction at age 5.

Sitnick et al. (under review) examined the duration of microsocial positive engagement and coercion for the dyad at child ages 2, 3, 4 and 5 years. These analyses do not address change in the momentary dynamics of parent



Note: Standardized β scores are reported. The following covariates were included in the analyses but are not shown for parsimony: family income, mother's education, child's gender, race, ethnicity, site location, and OPP/AGG at age 2. OPP/AGG = child oppositional-aggressive behavior, FCU = Family Check Up. $^{t}p < .10$, $^{*}p < .05$, $^{**}p < .01$.

Figure 15.4 A cross-lagged model for observed parent–child dyadic positive engagement and coercive interactions. *Source:* Adapted from S. Sitnick, D. Shaw, A. Gill, T. Dishion, C. Winter, R. Waller, . . . M. Wilson, *Parenting and the family check-up: Development and changes in observed parentchild interaction following early childhood intervention,* under review.

and child interactions. Systematically testing hypotheses on changing dynamics has long been a methodological challenge for researchers interested in social interaction patterns. Sequence was the core concept of a social interaction pattern. Much of the early work on coercion theory tested key hypotheses that a coercive event was contingent on an antecedent or was increased by a consequence, such as avoidance or escape. Analyses of contingency were fraught with methodological problems. For example, to analyze the conditional probability that a child's negative behavior is contingent on a mother's threats, it is necessary to examine the reactions to only 5% of the child's overall behavior in an observation session. Thus, 95% percent of the data on the child is tossed out in the analysis of sequences that involve reactions to child's negative behavior. The *z* scores derived from sequential analyses such as these were weak because of challenges in estimation of low base rate events (see Dishion & Granic, 2004; Gottman & Roy, 1990). In the past 5 years methodologists have applied a multilevel framework to improve the statistical estimation of dynamic events in social interaction (Dagne, Howe, Brown, & Muthén, 2002; Stoolmiller & Snyder, 2006). The multilevel framework promotes the estimation of latent constructs at the microsocial level. The most promising of these strategies is multilevel survival modeling, which takes into consideration the analysis of duration of events of interest. To oversimplify, the ability to systematically test hypotheses regarding the duration of specific interaction events increases the robustness of the estimators, because far more data are brought into estimates of dynamic events.

For example, Kim et al. (in preparation) were interested in the dynamic patterns of parent–child dyads illustrated in the state space grid shown in Figure 15.2. From a dynamic systems perspective, parent–child dyads who are not engaged in the coercion process are likely to show two dynamic patterns. The first is that if a dyad goes into the dyadic coercive state, they are likely to leave very quickly. Families who are not caught up in conflict avoid extended negative exchanges. Similarly, parent–child dyads engaged in positive and secure relationships are likely to return to dyadic positive engagement if they leave (see Figure 15.5). The statistical reliability of individual differences in these

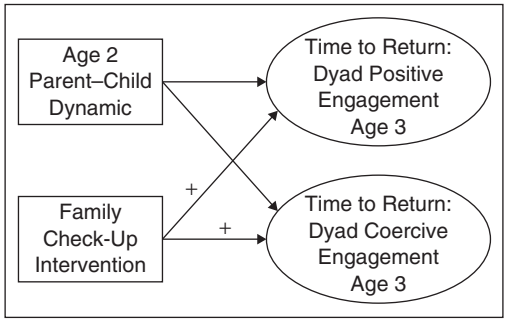


Figure 15.5 A multilevel analysis of intervention effects on family microsocial dynamics in early childhood. *Source:* Adapted from H. Kim, T. Dishion, J. Tein, C. Winter, D. Shaw, & M. Wilson, *Changing the microsocial dynamics of families: The family check-up in early childhood*, in preparation.

two dynamic patterns is estimated by using multilevel survival models. Kim et al. were particularly interested in whether randomization to the Family Check-Up (FCU; Dishion & Stromshak, 2007) intervention influenced these two microsocial dynamics from age 2 to 3. It was found that families in the intervention group were quicker to leave dyadic coercive states and also more rapidly returned to dyadic positive engagement, compared with control families. Thus brief feedback about parenting apparently changed parents' motivation and leadership to improve the positive exchanges and to reduce the duration of conflict.

These analyses suggest that the glass is half full for research on the coercion model in early childhood. The emerging coercion dynamic between children and caregivers is observable, predicts growth in noncompliance, and predicts that caregivers and teachers will perceive the youth to be problematic. The interaction process can be studied in real time, and the dynamics can be improved with a brief, strengths-based family intervention. Consistent with a developmental psychopathology framework (Cicchetti & Toth, 2009), broad constructs, such as conflict and attachment, can be translated to real-time dynamic relationship events (Granic & Patterson, 2006) that involve an analysis of the duration of interpersonal behaviors. From a microsocial view, attachment and coercion are not opposing theories, but rather are interrelated dynamic patterns in relationships. However, the effect sizes on coercive interaction dynamics are relatively small. Additional analyses of the factors related to change in parent–child coercion in early childhood revealed that these dynamics were most responsive in the FCU when therapists provided videotaped feedback to caregivers that showed their interaction dynamics (Smith et al., 2013). Given that coercive interactions are relatively low base rate and are often on "automatic pilot," more structure may be needed at the front end to motivate change with the FCU and follow-up services to change those overlearned interactions (Forgatch & Patterson, 2010).

Data such as these, however, provide considerable support for the hypothesis that how the parent reacts to their child's behavior can allay the development of early behavior problems and aggression. Of course, many randomized studies that targeted parenting practices have revealed consistent effects on reduction of aggression in early childhood; most noteworthy are the findings of Webster-Stratton and colleagues (Webster-Stratton & Reid, 2010). Recent studies have found that randomized assignment to the FCU resulted in improved child behavior and increased positive parenting (Dishion et al., 2008; Shaw, Dishion, Supplee, Gardner, & Arnds, 2006). In the Dishion et al., 2008, study, changes in parents' use of positive behavior support, observed during videotaped parent–child interactions, mediated the covariation between the intervention and reductions in child problem behavior from ages 2 to 4. Moreover, significant reductions were noted in teachers' ratings of oppositional defiance at age 7.5. In one study, the FCU, which was designed for use in public health or public school settings, was provided to families enrolled in the Women, Infants, and Children (WIC) program in three geographically distinct communities (urban, suburban, rural). Results revealed that the number of FCU interventions that a family completed increased the effect sizes on parent ratings of oppositional behavior and teacher ratings of problem behavior at age 7 (Dishion et al., 2014). Taken together, the findings suggest that parenting is indeed modifiable, and the benefits to children are pronounced and long-lasting.

MIDDLE CHILDHOOD: COERCION AND CONTAGION

Relevant to the cascade model (Figure 15.1), it is proposed that problem behavior in early childhood is prognostic of growth in new forms of such behaviors in childhood, including lying, stealing, and other covert behaviors. In the 1980s the field was concerned with potential specialization in children's antisocial behavior. Patterson's (1982) early work on coercion theory attempted to identify the unique family interaction profiles and treatment needs of children referred for stealing, distinct from those of children referred for aggression. This distinction was carried forward in an important review of the literature by Loeber and Schmaling (1985), in which the terms *overt* and *covert* antisocial behavior were coined. Several interesting studies compared the correlates of these two forms of antisocial behavior. It may be surprising that overt and covert antisocial behaviors have unique effects on children's lives, despite the fact that the two factors were correlated at about .8 in a community sample (Patterson et al., 1992). Loeber and Stouthamer-Loeber (1998) later clarified that involvement in both covert and overt antisocial behavior (mixed, early-onset) posed the greatest risk for more serious forms of violence and aggression in adolescence. These findings and conclusions were confirmed and extended in a comprehensive approach to longitudinal modeling that combined six data sets (Broidy et al., 2003). All six identified a group characterized by chronic antisocial behavior from childhood to early adolescence. In most youths, as Tremblay would hypothesize, aggression tended

to decrease over time (Tremblay, 2000). However, for the chronic group, the level of physical aggression remained stable. Interestingly, only for children in the urban sample, physical aggression actually increased from childhood to early adolescence, suggesting a contextual effect for the communities the youths resided in.

It has become increasingly clear that neighborhoods and communities have an influence on the peer group, which is readily observable in the context of neighborhoods and playgrounds. Coercion on the playground and deviant peer influence are observable in the first grade in the public school environment. It is interesting, however, that what is learned on the playground at school is only loosely associated with what the child has learned in the family. Examination of coercive dynamics with parents and those with peers on the playground has indicated a correlation of .19 between the two settings (Dishion, Duncan, Eddy, Fagot, & Fetrow, 1994). Thus it seems that interactions with peers potentially provide a relatively independent influence on the development and growth of antisocial behavior in childhood.

Research by Snyder and colleagues has provided insights about the role of peers in the growth of covert and overt antisocial behavior during childhood. These researchers developed a protocol that enabled the measurement of deviancy training among 5-year-olds in the school context (Snyder et al., 2005; Snyder et al., 2010). They found that deviancy training and coercion could be identified in peer interactions on the kindergarten playground. Moreover, as would be expected, coercive exchanges were associated with growth in overt forms of antisocial behavior in the ensuing year. That is, children who engaged with peers in a coercive manner were actually seen as more aggressive even by their parents, suggesting for the first time that there may be a carryover from peers to the family early in development. It previously had been assumed that the general direction of influence was from the family to peers (Patterson et al., 1992). Snyder and colleagues also found that deviancy training led to growth in covert antisocial behavior during the ensuing year, as seen by parents and by teachers. Covert and overt antisocial behaviors have been associated with a general tendency to engage in antisocial behavior at ages 7 and 8 (Snyder et al., 2008).

Figure 15.6 summarizes findings from the Snyder group (Snyder et al., 2010) regarding the general influence of deviancy training in kindergarten on subsequent development of antisocial behavior by age 9, based on youth report. Note that observed children's deviant talk in kindergarten independently predicted growth of antisocial behavior, controlling for the same behavior at age 5. These findings suggest that organization and structure of informal play settings in public elementary schools are key to learning antisocial behavior patterns that are prognostic of later aggression and violence.

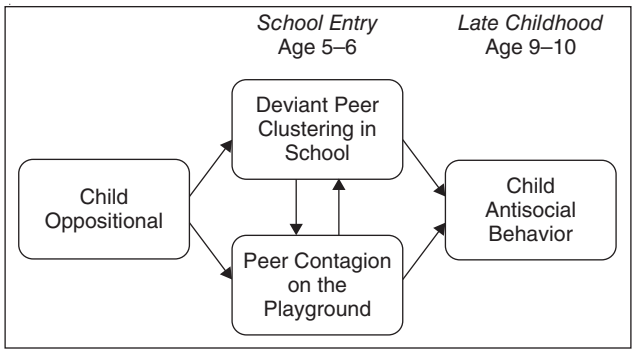


Figure 15.6 Peers and the emergence of covert antisocial behavior in middle childhood.

Several prevention trials have indicated that with relative ease, the public school environment can be modified to reduce ambient levels of peer aggression and antisocial behavior. For example, when teachers use the Good Behavior Game in classroom settings, levels of aggression drop at a group level; in addition, individual children who experience this intervention are less likely to become antisocial and violent (Kellam, Reid, & Balster, 2008; Petras et al., 2008). It is interesting to note that a relatively brief and focused contextual intervention in the first grade can have such a dramatic effect on growth of serious forms of antisocial and violent behavior in adolescence. As shown in Figure 15.1, relatively small improvements in microsocial interaction patterns can alter the child's adaptation in school and among peers, which in turn potentiates large reductions in risk over time.

Given the collateral effects of childhood antisocial behavior on several developmental outcomes, it is important to consider the evidence that it is malleable. Some intervention venues show success in reducing children's antisocial behavior. The first is to motivate and support caregiving behavior management and supervision. The vast majority of the research on parent management training, which has focused on conduct problems in middle childhood, has shown that supporting parenting practices reduces antisocial behavior (e.g., Kazdin, 2010). Especially noteworthy are the findings described by Forgatch and Patterson (2010), which showed effects endure for up to 9 years following intervention. Models of mediation have also revealed that improved parenting practices mediated long-term improvements in children's behavior that endured through adolescence, as documented by reduced

court-documented arrest rates. The second promising intervention venue is to work directly with the child, to motivate and support children's prosocial coping (Kazdin, 2010; Lochman, Boxmeyer, Powell, Barry, & Pardini, 2010). Both Kazdin's and Lochman's work provide empirical support for the idea that building youth skill in using prosocial strategies for resolving conflict and handling stress can reduce antisocial behavior.

ADOLESCENT PROBLEM BEHAVIOR

Peers and Sexual Selection

In a cascade developmental model, aggressive and antisocial behavior have collateral effects on normative peer relationships and academic achievement. Dodge and Coie's early studies inspired an entire era of research on peer rejection, and the covariation between aggressive behavior and peer rejection is well established. The aggressive child is quickly rejected by normative peers (Coie & Kupersmidt, 1983; Dodge, 1983). In my dissertation work, a general model was developed and tested that revealed that family interaction dynamics were prognostic of antisocial behavior and poor academic achievement, and both outcomes were prognostic of peer rejection (Dishion, 1990). Patterson tested the dual failure model, which added a depression overlay to concerns about the antisocial child, in that academic failure and peer rejection were found to be associated with depressed mood (Patterson & Stoolmiller, 1991).

Most relevant to the development of aggression and violence is the tendency to self-organize into deviant peer groups. In longitudinal research on the Oregon Youth Study sample, academic skill deficits, peer rejection, antisocial behavior, and poor parental monitoring combined to predict affiliation with deviant peers in early adolescence (Dishion, Patterson, Stoolmiller, & Skinner, 1991). Stoolmiller's (1990) work clarified that involvement with deviant peers was in part motivated by the child's behavior; in what was conceptualized as wandering, antisocial boys actually pulled themselves away from parental supervision and actively shopped for unsupervised settings and activities. This research prompted investigators to think of deviant peer affiliation as fitting the dynamic systems idea of self-organization. The biological and social changes associated with adolescence motivate youths to self-organize into groups, a process often studied intensively by social network researchers.

An evolutionary framework is critical to understanding what function is served when antisocial children self-organize into deviant peer clusters, beginning on the school playground in childhood and spreading to the community in adolescence and beyond. The vast majority of the research that seeks to understand the evolutionary function of social behavior in children emphasizes the role of harsh rearing environments in early childhood in adolescent pubertal development and adjustment (e.g., Belsky et al., 2010; Ellis et al., 2009). Primate studies, however, suggest that an overemphasis on the familial context and individual outcomes misses a critical aspect of the ecology of both normative and problematic development: the socializing influence of peers. Among primate adolescents approaching puberty, social interactions in the peer group define the process leading to status and dominance, both critical in later mate selection. In particular, among male rhesus macaques, puberty brings a demand to leave the matriarchal familial group and to form temporary adolescent peer groups. The timing of the departure depends on the social status of the mother, with low social status adolescents leaving earlier and higher social status adolescents leaving later. Thus social status of the mother confers risk to the offspring. An evolutionary-based correction factor for this disadvantage is adaptation to and survival in the all-male peer group. Thus males who survive the adolescent peer group phase enter a new troop, where status is renegotiated in the context of the dominant adult males in the new group. Presumably, status and dominance in the all-male peer group provides critical training for managing dominant males in the new troop. Thus the peer group functions to ensure survival of the fittest for the species, not the individual.

The peer group has often been posited to be critical for healthy social and emotional development (Piaget, 1965; Sullivan, 1953). Hartup and Moore (1990) brought to light the hypothesis that peers may be most influential when it comes to socializing problem behavior. As discussed earlier in this chapter, the contribution of peers to criminology was well accepted and acknowledged. Thinking about the role of peers in development from an evolutionary perspective, however, may bring new insights into previously unsolvable problems. One such problem was the age crime curve, in that across societies and cultures, youths tend to increase rule breaking, but the problem behavior decreases in young adulthood and is coincident with establishing new families (Gottfredson & Hirschi, 1990; Hirschi & Hindelang, 1983).

Two simultaneous trends co-occur during puberty that are particularly relevant to amplification of problem behavior during adolescence. This early-adolescence process, termed *premature autonomy,* involves pulling away from parental monitoring and influence at the same time

as seeking unsupervised time with peers (Dishion, Nelson, & Bullock, 2003). Youths whose parents disengage at the same time as they associate with other youths who promote deviancy are most likely to escalate in problem behavior from early adolescence to young adulthood.

Life history framework is a model of development that integrates environmental disruption with an evolutionary perspective on development (Ellis et al., 2009). Belsky et al. (1991) initially used the life history framework to understand individual differences in child and adolescent social and emotional adjustment and emphasized female development, puberty, and early sexual promiscuity. The concept is that stressful early child-rearing environments, especially those characterized by harshness and unpredictability (e.g., social disadvantage, marital instability, family conflict), evoke fast life history strategies, which are characterized by early menarche, early sexual involvement, and early and frequent childbearing and low-investment parenting. In contrast, safe, secure, and predictable child-rearing environments (e.g., adequate socioeconomic resources, marital stability, supportive parent–child relationships) promote slow life history strategies characterized by later onset sexual behavior, later puberty, enduring monogamous relationships, fewer and later offspring, and high-investment parenting strategies.

Introduction of the life history framework to developmental psychology opened the door to novel hypotheses regarding the links between childhood experiences, tempo of pubertal development, and concomitant reproductive strategies (see Belsky, Steinberg, Houts, Halpern-Felsher, & NICHD Early Child Care Research Network US, 1991; Ellis et al., 2009). The life history framework was recently applied to a longitudinal sample of females followed from early childhood through adolescence. In support of life history theory, the researchers found that maternal harshness at age 5 predicted the child's early menarche, which in turn predicted sexual risk taking and other problem behaviors, such as substance use (Belsky et al., 2010; see also James, Ellis, Schlomer, & Garber, 2012). The model fit the data for females, but a model for males has not yet been tested.

A significant omission from the life history framework is the function of peer clustering in early to middle adolescence with regard to regulating reproductive strategies. As described earlier, children and adolescents tend to self-organize into peer groups based on similarities of attitudes, behavior, and circumstances, and those interpersonal dynamics of peer contagion tend to amplify various forms of problem behavior (Dishion & Tipsord, 2011). Most important for a life history perspective, deviant peer clustering has been found to consistently be the strongest predictor of early and promiscuous sexual activity in adolescence, over and above pubertal maturation of males or females (Capaldi, Crosby, & Stoolmiller, 1996; French & Dishion, 2003). High peer group status is important in several primate species (de Waal, 2006). Primate studies demonstrate that peers not only serve a repair function for maternal deprivation (Suomi & Ripp, 1983), but also as a socialization nexus between early maternal rearing and adolescent mate selection and production of offspring (Kohler & Gumerman, 2000; Sameroff & Suomi, 1996).

Pellegrini and colleagues completed a creative longitudinal study that followed 138 early-adolescence males and females during their first 2 years of public middle school (Pellegrini & Long, 2003). Of interest were the peer dynamics among males and females that defined the basis for dating popularity in early adolescence. In their analysis the researchers included observable behaviors, such as poking play during unstructured school hours, as well as peer nominations of relational aggression, dominance, and dating popularity. The study found that for girls, high levels of relational aggression accompanied increases in dating popularity, whereas for boys, high levels of dominance accompanied increases in dating popularity. Consistent with sexual selection theory (e.g., Trivers, 1972), these results suggest that intrasexual competition was played out by gender-specific forms of problem behavior, which in turn increased the likelihood of sexual relationships in early adolescence.

If self-organization into peer groups is critical to sexual selection, a developmental history of marginal peer relationships and attenuated family ties may be particularly salient as an ecology that promotes the formation of deviant peer groups. Youths with a history of marginalization in school by teachers and peers, with attenuated family ties, and with low socioeconomic status would most likely self-organize into groups. These groups would naturally support adult-like behaviors that are correlated with mate selection and sexual activity in adulthood.

Dishion and colleagues used longitudinal data to examine whether the peer-enhanced life history perspective accounted for differences in deviant peer clustering in early adolescence, which in turn predicted both sexual activity and timing and number of children (Dishion et al., 2012). The model shown in Figure 15.7 was tested on a multiethnic sample of males and females followed from age 11 through age 24. In general, the model fit the data well, and there were no differences in fit for males and females or for European American or African American adolescents. As predicted, a history of peer and teacher rejection in middle school, along with attenuated family ties (low monitoring, involvement, positive parenting)

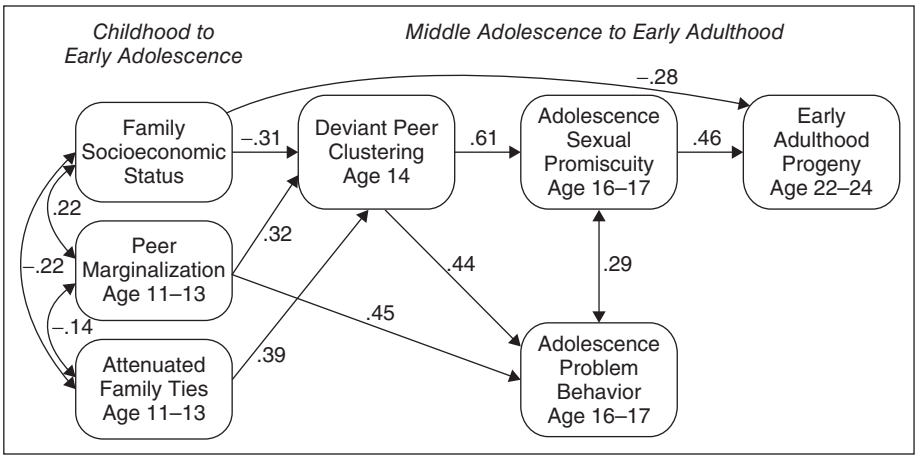


Figure 15.7 Life history perspective on peer influence in adolescence.

combined to predict self-organization into gangs by age 14. Deviant peer clustering at age 14 predicted sexual promiscuity by age 16–17, which in turn predicted the number of children by young adulthood. Of interest to the life history perspective was that deviant peer clustering predicted later sexual promiscuity ($\beta = .61$) more than did problem behavior ($\beta = .41$) by age 16.

These findings support the theory that the child's ecology and developmental history predict motivation to self-organize into groups and that such groups could be seen as functional to procreation. Consistent with the fast life history pathway, having more children more quickly may even the playing field from an overall fitness coefficient. Although the dynamic shown in Figure 15.7 is primarily social, it is hypothesized that future research will suggest that the changes are epigenetic. A relatively underemphasized dimension of environmental threat for human and nonhuman primates is exclusion, marginalization, and rejection (de Waal, 2009). Evidence suggests that threats of rejection, even during simple lab tasks, elicit strong reactions of emotional distress, as evidenced by amygdala activation (Eisenberger, Lieberman, & Williams, 2003). Therefore, a sense of isolation, exclusion, and social disadvantage may elicit mutual interest in forming subgroups among youths with similar circumstances.

Early adolescence may be a particularly critical period for concerns of social inclusion and exclusion. Physiological changes in the developing brain during adolescence suggest the importance of peers. The primacy of the peer group in adolescence is supported by a shift in the physiological substrate and in cortical processing that affects the salience and experience of social rewards (Spear, 2010). Several patterns of neuroanatomical response indicate increased processing of social reward during adolescence (Dahl, 2004; Fareri, Martin, & Delgado, 2008; Spear, 2000), which suggests an enhanced desire and potential for peer group affiliation. The consequences of peer marginalization and attenuated family ties, therefore, may be particularly salient motivations for the formation of deviant peer clusters.

It is likely that the model tested in Figure 15.7 is most salient for youths with an early-onset developmental trajectory of antisocial and problem behavior. As described in early- versus late-onset models, early-onset youths may actually gain status vis-à-vis their problem behavior in the peer group, with late starters following suit by imitation and deviancy training (Moffitt, 1993). One of the challenges of a developmental model of problem behavior is to account for the covariation between deviant peer networks and various forms of problem behavior in adolescence. As summarized in Figure 15.8, the adolescent peer group is associated with escalations in drug use, violence, and sexual activity.

There is a fork in the developmental pathway for adolescent peer influence. One path leads to increases in

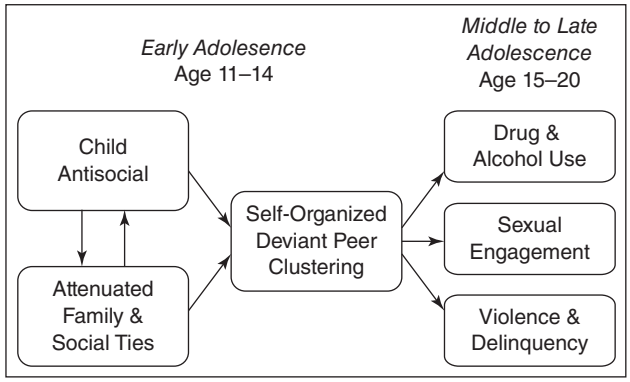


Figure 15.8 Self-organized peer groups and adolescent problem behavior.

the seriousness of aggression and to violence. In early adolescence, aggression can become a salient strategy for friendship selection and social status (Logis, Rodkin et al, 2013; Rulison et al., 2013). The formation of gangs in early adolescence creates a peer context in some ecologies that promotes aggressive responses to provocation and rejection. The second developmental pathway leads to adolescent substance use. Relatively well-adjusted adolescents may initiate alcohol and other drug use as a strategy for developing a peer group context that is highly rewarding and autonomous from parents (see Light et al, 2013). Indeed, growth in popularity over time is associated with growth in alcohol use (Osgood et al., 2013). A careful examination of the nature and quality of the friendships and the microsocial interactions therein provides clues about the processes by which these two pathways lead to dramatic differences in developmental outcomes by young adulthood.

Peers and Substance Use

It is likely the shift in sensitivity to social rewards in puberty renders youths vulnerable to both marginalization and influence in the context of friendships (Steinberg et al., 2006). One of the most effective strategies for expanding one's social network is to share alcohol and drug use (ADU). Legal drugs, such as tobacco and alcohol, are easy venues for early adolescents to mutually explore and engage in adult-like, rewarding activities. An especially vulnerable time for young adolescents is the hours after school, when youths have ample opportunity to smoke or drink in settings without adults (Friedman, Lichtenstein, & Biglan, 1985). The number of hours unsupervised with peers is the best predictor of escalations in tobacco, alcohol, and marijuana use between ages 12 and 15 (Dishion, Bullock, & Kiesner, 2008). Youths self-organize into informal groups and gatherings to explore the rewarding properties of substances and social connection, and they collude to avoid detection and adult sanctions (Dishion & Bullock, 2002; Stoolmiller, 1990). Pulling away from adult supervision to engage in rewarding social and sexual activities during puberty is surely an ancient human primate practice that is unlikely to change.

Unfortunately, use of substances by age 15 is highly prognostic of developing alcohol and drug dependence by young adulthood (Anthony, 1991; Robins & Pryzbeck, 1985). Early-onset and persistent substance use can undermine achievement of adult milestones and healthy adult adaptation (Kandel, Davies, Karus, & Yamaguchi, 1986; Yamaguchi & Kandel, 1985). A critical question for developmental and intervention theory is whether some youths are more vulnerable genetically to moving from adolescent exploratory use to addiction. Although the evidence is clear for a genetic liability (see Grigorenko & Dozier, 2013), it remains unclear whether it is specific to addiction or to impulsive behavior in general (Beauchaine & Hinshaw, 2008; Dick et al., 2009; Kalivas & Volkow, 2005). Evidence does suggest that the progression to ADU dependence from early-adolescence problem behavior indicates unique dynamics within the peer group.

Research on early pathways leading to substance use supports the cascading developmental model summarized in Figure 15.1, with antisocial problem behavior preceding the onset of smoking, alcohol, and marijuana use (Dishion, Capaldi, & Yoeger, 1999; G. M. Smith & Fogg, 1979). A substantial body of research has established the importance of neighborhood environments for child and family development (Leventhal & Brooks-Gunn, 2000; Shonkoff & Phillips, 2002), particularly for youth problem behavior and specifically for youths living in high-risk, low-income neighborhoods characterized by disadvantage and residential instability (Coley, Morris, & Hernandez, 2004; Hawkins, Van Horn, & Arthur, 2003), low collective efficacy (Sampson, Raudenbush, & Earls, 1997), and presence of deviant peers and adults (Ingoldsby, Shaw, Winslow, Schonberg, & Gilliom, 2006). ADU is not confined to youths in disadvantaged settings or youths of minority status, however. Several studies have identified European American youths as having the most pervasive ADU, and youths in families with high socioeconomic status are often quite vulnerable to high levels of ADU (Luthar & Barkin, 2012).

Ecological conditions and genetic vulnerability to develop ADU problems appear to be moderated by parenting practices, such as monitoring and contact and engagement with drug-using peers. Shaw et al. (2004) reported that deviant peer clustering attenuated the effects of parental monitoring and limit setting on youth problem behavior in the highest risk, low-income urban neighborhoods. Already-classic work by Dick and colleagues (2009) found that increased risk for a variety of problem behaviors in adolescence, including substance use, is associated with the GABRA2 polymorphism. However, those youths with genetic liability who were monitored well by parents showed no vulnerability toward engaging in these problem behaviors. Systematic prevention research by Brody and colleagues (2009) revealed that random assignment to a family-centered prevention program reduced the effects of genetic liability for adolescent substance use.

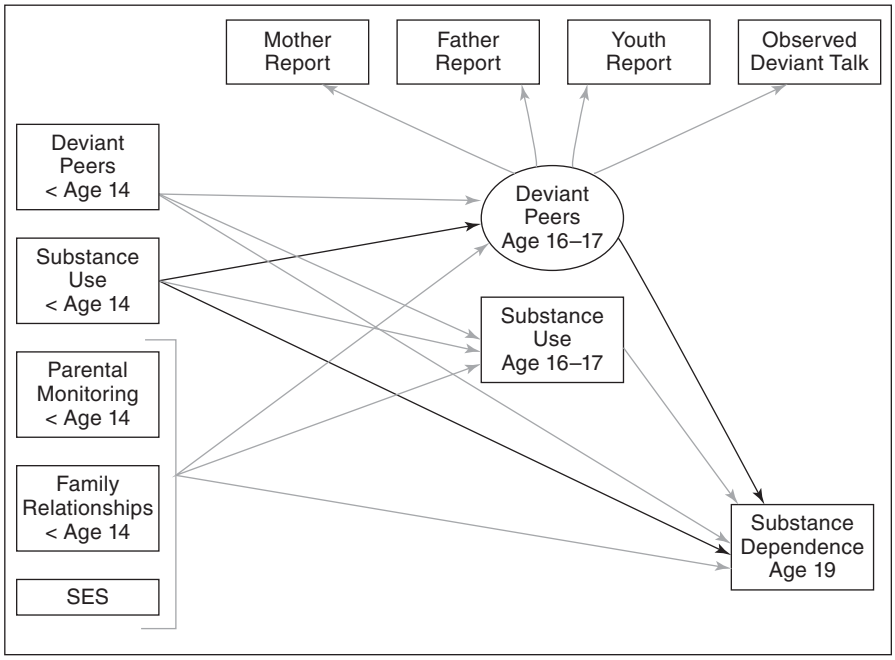


Figure 15.9 Self-organized peer groups and progressions to adolescent ADU dependence. *Source:* Adapted from M. J. Van Ryzin & T. J. Dishion, Adolescent deviant peer clustering as an amplifying mechanism underlying the progression from early substance use to dependence, *Journal of Child Psychology and Psychiatry,* 2014, pp 667.

My colleagues and I have intensively studied the contribution of the peer network and friendship dynamics on the progression from ADU in early adolescence to ADU dependence by early adulthood. In a sample of 998 ethnically diverse youth (males and females), we examined the progression from early-adolescence use to dependence by age 19 (Van Ryzin & Dishion, 2012). As found in previous studies, European American males were the most likely to initially use tobacco, alcohol, and marijuana and not surprisingly, progress to dependence by age 19. We were interested in the role played by deviant peer clustering in the progression from early use to dependence by age 19 (Figure 15.9). By studying the progression of tobacco, alcohol, and marijuana use separately, we examined the dynamics of drug-using friendships in the progression to dependence, controlling for early use and parental monitoring. The construct measuring deviant peer clustering at age 16–17 was defined by parent, youth, and teacher report and by direct observations of the youth and friend's deviant talk (Dishion, Capaldi, et al., 1995).

The results of these three longitudinal models are summarized in Table 15.1. For each substance, we found early use to be a robust predictor of progression to dependence by age 19. However, in addition to the effects of early use, deviant peer clustering was by far the strongest predictor. Thus becoming addicted to tobacco, alcohol, and marijuana as a youth is strongly associated with the company

TABLE 15.1 Peer Clustering on ADU as a Mediator for Progressing to Late-Adolescence Dependence

Predictors	Nicotine dependence	Alcohol dependence	Marijuana dependence	Deviant peer affiliation (ages 16–17)
Deviant peer affiliation (ages 16–17)	11.71[1]	14.68[2]	11.80[1]	—
Substance use (ages 16–17)	1.14[1]	1.14[1]	1.15[1]	—
Early tobacco use	1.19	1.46	.98	.25[3](.06)
Early alcohol use	.93	.48	.97	.05(.05)
Early marijuana use	.97	.61	1.11	.14(.07)
Early parental monitoring	1.01	1.37	1.35	−.07[2](.03)
Early family relations	1.39	.98	1.35	−.03(.03)
Early deviant peer affiliation	.70	.55	.70	.08[3](.02)
Socioeconomic status	1.27	.59	1.35	.02(.03)

[1] $p < .05$
[2] $p < .01$;
[3] $p < .001$
Source: Adapted from M. J. Van Ryzin & T. J. Dishion, Adolescent deviant peer clustering as an amplifying mechanism underlying the progression from early substance use to dependence, *Journal of Child Psychology and Psychiatry,* 2014, pp. 6.

one keeps. In previous research, it was found that the covariation between use of tobacco, alcohol, and marijuana and friendship selection and influence was bidirectional. Early use predicted the selection of friends on the basis of conversations about drug use and deviant behavior. In turn, selecting a friend who engages in these discussions uniquely predicts escalation in the use pattern (Dishion & Owen, 2002).

One can think of friendship selection and influence as a process of joining. Finding common ground and mutual interests is one way to connect with a potential friend. Thus, for a smoker, pulling out a cigarette and smoking together could be seen as joining around tobacco use. Undoubtedly many friendships are established this way, around the use of a specific substance, and some may progress to be satisfying relationships that include other interests and activities besides substance use. Relationship dynamics that account for socialization and influence are of special interest to the peer relationship field (see Bukowski, Pizzamiglio, Newcomb, & Hoza, 1996; Hartup, 1996). The quality of the friendship would seem to enhance the power of the friendship to influence youths toward ADU. However, youths more prone to ADU are perhaps less likely to have high-quality friendships, because of underlying antisocial behavior. Thus, friendship quality might be a sign of positive adaptation and potentially an indicator of less risk for ADU progression.

One of the problems in measuring friendship quality is that global reports may be biased with respect to the youth's need for a friend. Those who are more desperate for a friend may be more disposed toward endorsing any friendship as desirable. To avoid this difficulty, Piehler carefully observed the friendship dynamics of the Project Alliance sample ($N = 998$), who were videotaped while interacting with their close friends at age 16–17 (Piehler & Dishion, 2014). He coded their ability to coregulate during the course of their 40-minute videotaped interaction task, which included their ability to take turns talking, to mutually reference each other's discussion topics, facilitate the discussion with eye contact and head nodding, and to remain attentive to the discussion. Coders were highly reliable in coding coregulation and duration of deviant talk.

Dyadic coregulation was found to moderate the covariation between observed deviant talk and progression in drug use from age 16 to 19. However, the nature of the moderation was opposite of what had been expected (Figure 15.10). Stronger covariation was found between deviant talk and later drug use in the friendships that were highly coregulated. Friendships that were less coregulated tended to be less likely to progress toward more serious use by age 19. The basic conclusions are summarized in Figure 15.11. Youths in friendships that are coregulated and that include talk about ADU are the most influential

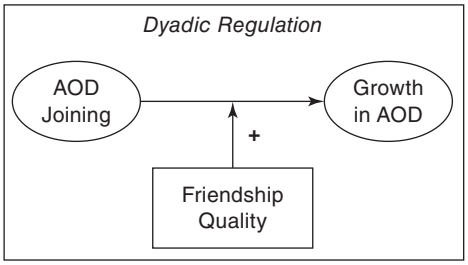


Figure 15.10 Adolescent friendship influence on the ADU progression.

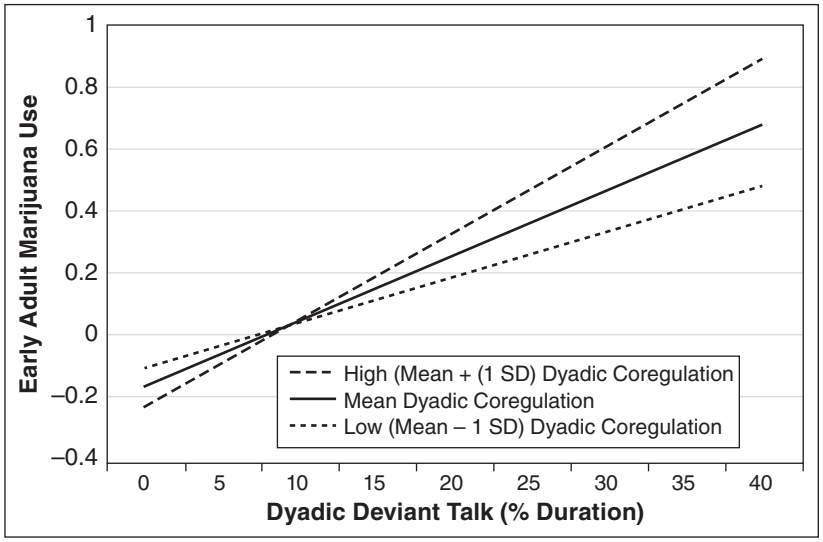


Figure 15.11 Dyadic coregulation as a moderator for friendship influence progressions in substance use.

for progression of ADU. These findings square with earlier research (Dishion, Nelson, & Bullock, 2004) on the moderation of deviancy training at ages 13–14 on later antisocial behavior (ages 23–24). Friendships that were dynamically more organized and engaged in deviant talk were more prognostic of escalations in problem behavior through young adulthood.

Piehler followed up on these findings to better understand the link between individual vulnerability and friendship influence. When the youths were young adults (ages 22 and 23), their ADU and dependence were again assessed (Piehler, Véronneau, & Dishion, 2012). These models included a multiagent construct of effortful control, also measured at ages 16–17, along with a construct measuring friendship drug use at the same age and prior levels of drug use. In these models, it was again hypothesized that high levels of effortful control would moderate the influence of friends on ADU progression. However, no such interaction was found. Prior substance use, friendship influence, and effortful control all predicted progression from ADU to problematic use in early adulthood, with effortful control predicting less use.

These findings suggest that an individualistic model of adolescent ADU progression is likely to be incomplete and insufficient for guiding prevention. Research on the etiology and progression of ADU has clarified that the developmental and interpersonal dynamics of adolescence ADU are very different from the dynamics of aggression and violence. ADU is a strategy for expanding one's social friendships and engaging peers in the context of rewarding activities. Although early antisocial behavior and aggression are prognostic of early-adolescence initiation, it is clear that ADU behaviors are about reward: pharmacological, social, and sexual. Future research will clarify if ADU actually provides the antisocial adolescent with a venue for learning social skills that were underdeveloped in childhood. ADU in adolescence, however, presents the significant challenge of self-regulation of reward. As we have seen, the inability to regulate the rewarding properties of ADU leads to dependence and addiction in early adulthood.

Coercive Joining and Violence

One of the most perplexing problems for criminology is predicting movement from being a troublesome child to becoming a violent offender. The vast majority of research about this transition suggests simply that early-onset youths with high rates of antisocial behavior are those who progress to violence in late adolescence and young adulthood (Capaldi & Patterson, 1996; Farrington, 1991; Loeber & Farrington, 1998; Monahan, 1978). However, most early-onset antisocial youths do not progress to being violent offenders. Quite the opposite, there is a general downward trend in aggressive behavior from childhood through adolescence, except for those youths living in a high-risk urban setting (Broidy et al., 2003).

There is some evidence that escalation from antisocial tendencies to violent offending involves peer group macro- and microsocial processes. At the macro level, self-organization into gangs provides ample support for violent behavior. Systematic longitudinal research on gangs has revealed surges in violent and other forms of problem behavior during the time youths identify and associate with gangs (Thornberry, 1998). In early research on deviancy training, it was found that longer durations of deviant talk and discussions of violence in 30-minute videotaped interactions uniquely predicted later arrests for violent offending (Dishion, Eddy, Haas, & Spracklen, 1997).

Another approach to longitudinal data is to model trajectories of peer groups and map onto those groups longitudinal changes in antisocial behavior. When Lacourse and colleagues used this strategy, they found that the youths who increased their violent behavior were those who were in the chronically deviant peer group from childhood through adolescence (Lacourse, Nagin, Tremblay, Vitaro, & Claes, 2003). These data suggest that the passage from troublesome to dangerous is by and large not a solitary endeavor and that some peer groups cocreate violence.

The cascading developmental process has been tested in several longitudinal studies and found to be prognostic of adolescent violence (Dishion, Véronneau, & Myers, 2010; Dodge et al., 2008). As described previously, marginalized youth with attenuated family ties are more likely to self-organize into gangs, which in turn, support aggressive and violent acts. Given the consequences, it is essential to know which youths are more vulnerable to gang membership. As one might expect, gangs are more prevalent in specific communities. From a historical perspective, poor and disorganized communities with pockets of marginalized individuals tend to have high rates of crime and gang structures (Sampson & Laub, 1994). For example, Sampson & Laub (1994) reported that in early nineteenth century Boston, Irish immigrants were more likely to be involved in crime and gang activity.

The friendship dynamics that define the deviant peer group determine in part what becomes socialized in the group. When my colleagues and I first intensively studied friendship dynamics, we focused on a sample of mostly European American boys from a suburban community. We

were surprised to find very little negativity or aggression in the friendship interactions (Dishion, Andrews, & Crosby, 1995). Only a handful of the 204 boys participated in coercive exchanges with friends during an observation task. Consequently, we focused primarily on the role of positive reinforcement (i.e., laughter) in supporting deviant talk (i.e., deviancy training). However, when we later analyzed friendship interactions among an urban sample of youths, the picture changed. Significantly more than a handful of friendships were characterized by a mutually aggressive posture and overt efforts to exert and maintain dominance over one another. It did not take a rocket scientist to see a connection to gang involvement, in that many of the youths in the friendship interactions were dressed in gang attire and used gang-like mannerisms. We became interested in the idea that specific social interaction patterns presented a coercive stance to the social world that amplified a youth's tendency to become violent in late adolescence to early adulthood. That is, they would become dangerous people.

We came to term the process we had been witnessing *coercive joining*; that is, a friendship of two individuals is organized in terms of coercing others primarily and each other secondarily. When coercion is the organizing theme, the individual who is more likely to escalate in aversiveness or dangerousness (e.g., physical aggression, assault) is the one who has the most influence. Moreover, the dyad is made stronger by joining in coercion; that is, they coerce others and take pride and enjoyment in treating others abusively or with aggression. As is often documented in the gang literature, the ability to be fearless and highly aggressive is directly linked to status in the group (Raine, 2002). Being able to regulate emotion during a dangerous fight and to assault your opponent is valued by the peer group. Recent research on the macrodynamics of adolescent aggression has revealed that status in the peer network is a driving mechanism for the maintenance and amplification of aggression in early adolescence. For example, in urban New York City, changes in social status within the peer network are associated with carrying weapons (Dijkstra et al., 2010).

We were interested in studying the microsocial dynamics within adolescent friendships that might map onto network findings about the role of status. Is it possible that adolescents who are prone to escalating violence actually select and socialize one another to be more violent? In our multiethnic sample of 998 adolescents, we found that indeed, high levels of observed coercive joining uniquely predicted movement from antisocial behavior to violence by early adulthood (Dishion & Van Ryzin, 2011). Violence was defined by multiple indicators, including violent arrests, self-reports of carrying weapons, mother and father report, and self-reported aggression. Observed coercive joining was measured in 40 minutes of videotaped friendship interaction and included youths' efforts to dominant one another, talk that promoted the abuse of others, and profanity. Observed coercive joining accounted for substantial unique variance in later violence more than did antisocial behavior measured at the same time.

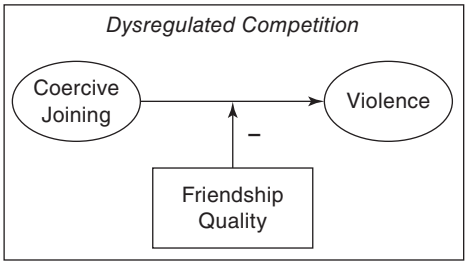


Figure 15.12 Adolescent friendship influence on violence progression.

We were next interested in whether the quality of the friendship moderated the influence of coercive joining on later violence. We suspected that poor-quality friendships were actually prognostic of socialization of violence in friendships (Figure 15.12). If such friendships are motivated by status in the peer network, then they are a sign and symptom of a friendship of convenience. A friendship of convenience is one that is easily available by means of proximity, such as the same neighborhood. In previous research on another sample, it was found that early starters were more likely to select friends from the same neighborhood (Dishion, Andrews, et al., 1995). To examine their friendship quality, each youth was asked to report about their satisfaction with the friendship, pleasant activities they shared, and the extent to which they agreed about basic friendship issues. In a model that included antisocial behavior at ages 16–17 and coercive joining and friendship quality that predicted serious violence by ages 22–23, all three predictors were statistically reliable. As one might expect, an interaction effect was found between friendship quality and coercive joining, and youths with the lowest friendship quality and the highest levels of coercive joining were the most violent 5 years later. Coercion in friendships undermines the relationship and socializes youths to become increasingly dangerous.

Youths with a long history of behavioral difficulties and marginalization are likely to have also accumulated traumatic experiences that disrupt emotional regulation and that can potentially amplify aggression in the face of conflict. Research by Gorman-Smith and Tolan (1998) suggests that trauma in violent communities begets violence.

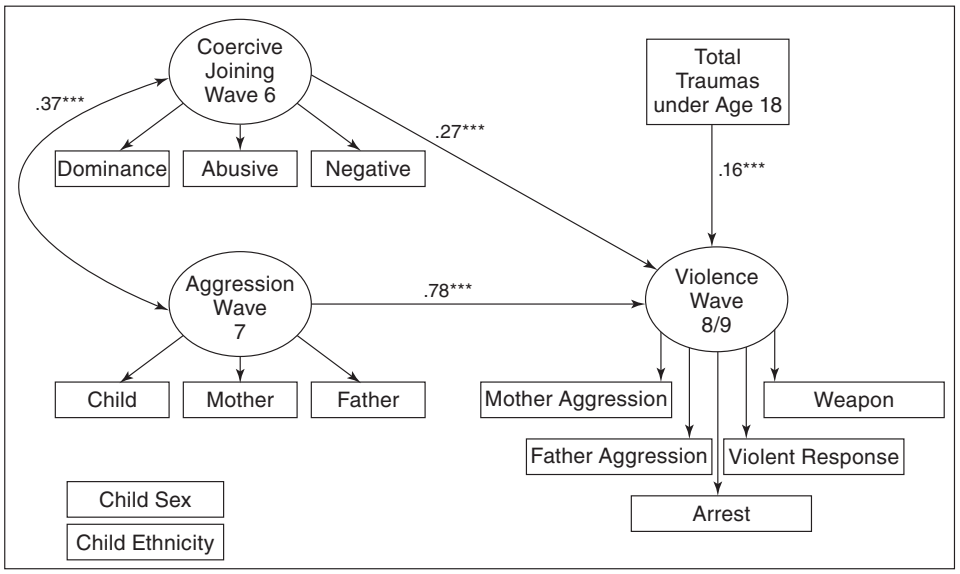


Figure 15.13 Unique contributions of trauma to adolescent violence. *Source:* Adapted from Dishion & Zerr, in preparation.

When the youths were age 18–19, they were queried about their retrospective history of traumatic experiences, including exposure to violence in the community and betrayal by a significant other (Freyd, 1996). The total self-reports of trauma indeed accounted for unique variation in later violent offending, controlling for coercive joining in the friendship and aggression at age 17 (see Figure 15.13). Interestingly, when traumatic experiences were divided between betrayal and community violence, the number of traumatic experiences that involved an interpersonal betrayal accounted for variation in later violence. Such traumas include sexual abuse by trusted others and other abusive experiences by family members.

Involvement in coercive dynamics with friends and continued aggression is best understood by looking at the family–peer ecology. It has been hypothesized that youths who were observed in coercive interactions with family members in early adolescence would most likely be those who engaged coercively in the peer group, which in turn would predict amplification to violence by adulthood. The coercion model suggests that coercive interaction patterns in families provide the basic training for youths to feel comfortable establishing coercive friendships (Figure 15.14). This hypothesis was tested with a subset of the sample described earlier, who were preselected to also complete family observation tasks when they were young adolescents (Van Ryzin & Dishion, 2012). Coercive interactions within the family were prognostic of later coercive joining in friendships, which in turn predicted violence in young adulthood, controlling for previous levels of antisocial behavior and even observed deviancy training with friends at ages 16–17. The covariation between observed coercion in the family at ages 12–13 and acting out dangerous behaviors 10 years later was mediated by coercive joining with friends at age 16.

Yet another question about the development of violence requires more research: To what extent is violence reinforcing? Systematic research revealed that when young children countered aggression on the playground with more intense aggression, the behavior was reinforced and led to more aggression later (e.g., Patterson, Littman, & Bricker, 1967). For some youths, dangerous threats or acts are reinforcing at an individual and group level. For example, in some contexts, an attack on a victim that leads to death or submission can positively affect the status of the offender in a violent community. The person most willing to face potential danger to self in the process of harming others is revered as dangerous or bad. Such a process can be realized only when the ambient level of violence is high, such as in a gang or in the context of war (Patterson, 2012). Ellis and colleagues (Ellis et al., 2012) similarly point out that in bullying behavior in early adolescence, the bully gains status. The entry card is risking one's own safety to inflict harm on others.

If violence is understood as individually reinforcing with respect to social status, current interventions designed to reduce antisocial behavior at younger ages may have only limited effectiveness. In Project Alliance 1, 999 11-year-olds were individually randomized to either middle school as usual or middle school with the offer

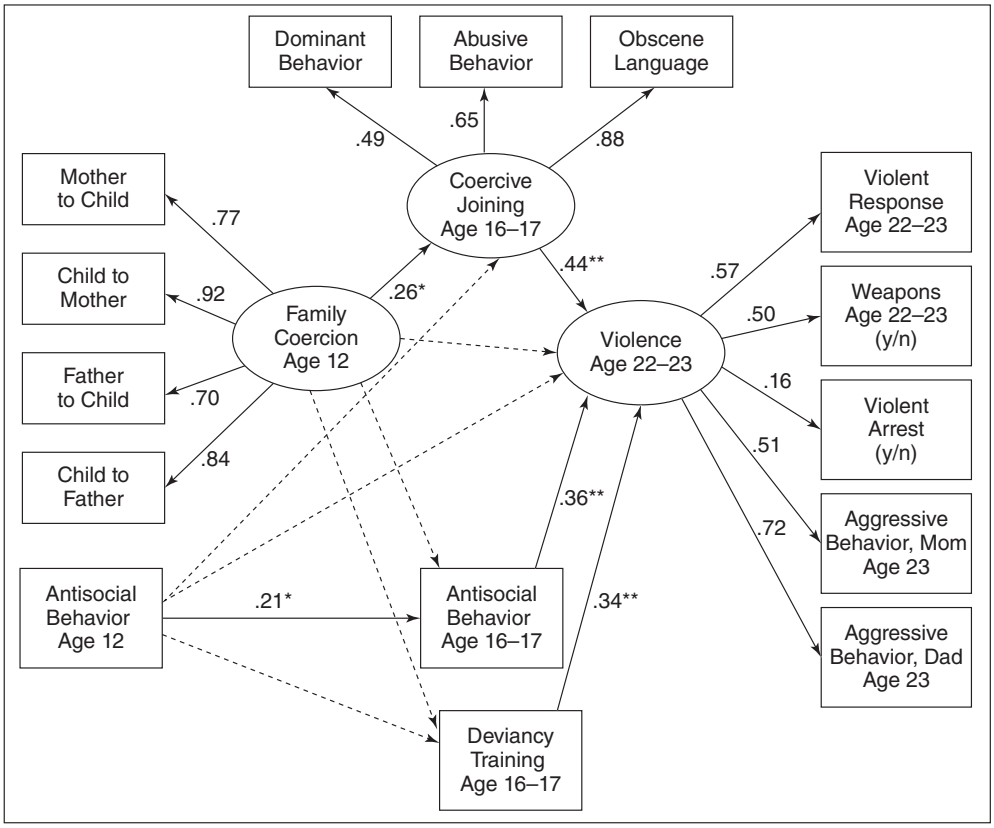


Figure 15.14 From family to peers: microsocial coercion in the development of violence.

of an FCU. Of the families assigned to the intervention group, 25% agreed to engage in the FCU. Using intention-to-treat analyses, we found that participation in the FCU was associated with reduced substance use (Dishion, Kavanagh, Schneiger, Nelson, & Kaufman, 2002), and for high-risk youths, changes in substance use were associated with improved parental monitoring practices (Dishion, Nelson, & Kavanagh, 2003). Our research team later found that antisocial behavior by age 18 was reduced for those in the intervention group, an outcome that was partially mediated by long-term reductions in parent–adolescent conflict (Van Ryzin & Dishion, 2012). Using mixture modeling longitudinal data analysis, it was found that randomization to the FCU reduced serious forms of antisocial behavior, including arrests (Connell, Dishion, Yasui, & Kavanagh, 2007). The intervention, on the other hand, did not prevent serious violence.

It is generally the case that randomized intervention studies provide only limited evidence that adolescent violence can be reduced through intensive, family-centered interventions (Henggeler & Schaeffer, 2010). Adolescent involvement in gangs seems particularly intractable. Malcolm Klein, whose career focused on understanding and intervening with adolescent delinquent gangs, concluded that the best approach is to prevent gangs from forming rather than try to reduce gang influence after they have formed (Klein, 2006).

SUMMARY AND FUTURE DIRECTIONS

Decades of research in development and psychopathology are providing an empirical account of how some children move from minor problems in self-regulation and problem behavior to more serious problem behaviors, such as ADU, high-risk sexual behavior, illegal behavior, and violence. One of the most surprising outcomes of the past decade of research on antisocial behavior is the lack of gender differences in the etiology of problem behavior (Miller, Loeber, & Hipwell, 2009; Odgers et al., 2012). In our developmental and intervention models in early childhood, my colleagues and I have found that intervention effects and key environmental factors are at play for both males and females. Moreover, we have not found major differences in the structure of risk factors across African American, European American, and Latino families to

date, despite the resource and health inequities observed (Trentacosta & Shaw, 2009). The major gender difference is that more males are identified as early-onset persistent in their antisocial behavior (Odger et al, 2012), which is consistent with the fact that more males are referred to clinical services and come into contact with juvenile courts than do females. There is some evidence from behavior genetic research that heritability of antisocial behavior is somewhat higher in males than in females (Meier et al., 2011), and this accounts for the high levels of stability often seen in male aggression (Olweus, 1983).

Clearly, there are deep gender differences with respect to male and female social networks, the role of romantic relationships and sexuality, and the need to drop out of the deviance process because of pregnancy and childbirth. Of interest is the finding that academic failure and peer rejection predict gang membership for boys and for girls. However, ratings of being liked were predictive of gang membership only for boys, suggesting that social status of potential gang members is high among males in early adolescence. One problem with research on gender differences with regard to various forms of problem behavior is that the environmental constructs measured are often rather crude, in that they often define global parenting and peer constructs by means of youth or parent report. Direct observation of male and female behavior within contexts that pull for gender differences might yield more promising results. The naturalistic observation research by Pellegrini and Long (2003) is one example, in that the predating play within the context of unstructured time in public schools yielded rather striking gender differences specific to sexual selection theory.

Dishion and Patterson (2006) reviewed the emerging literature about self-regulation in general and effortful control (Rothbart, 2012) in particular accounting for the etiology of problem behavior in childhood and adolescence. Conceptually, difficulties in self-regulation and effortful control seem to be obvious candidates for explaining the timing and course of antisocial and other problem behaviors. Moreover, several evidence-based interventions that specifically target children's self-regulation show moderate effect sizes (e.g., Kazdin, 2010; Lochman et al., 2010). A handful of studies in the last review (Dishion & Patterson, 2006) indicated that child and adolescent self-regulation could moderate the impact of pathogenic environments on later outcomes, thus empirically defining the critical construct of resilience (Luthar, 1991; Masten & Coatsworth, 1998; Zautra, 2009). The moderation framework is in agreement with the differential susceptibility hypothesis, which proposes that vulnerable children are more responsive to positive environments and reactive to pathogenic environments (Belsky & Pluess, 2009). The differential susceptibility hypothesis, therefore, is an optimistic stance that does seem to fit with some of the data. For example, several prevention scientists are finding that interventions that effectively change the environment seem to have the most pronounced effects on those youths who are at highest risk initially (Bierman et al., 2010; Connell et al., 2007; Dishion et al., 2008; Forgatch & Patterson, 2010).

There continue to be problems, however, in the constructs of dysregulation, self-regulation, or emotion-related self-regulation that require attention in future research. Aside from the conceptual overlap with problem behavior, the measure of these constructs must be further refined along the lines suggested by Beauchaine, Hinshaw, and Gatzke-Kopp (2008), with particular focus on vulnerability to reward and on the dopamine system. Much of the work on self-regulation occurs in a motivational vacuum, with low levels of reward in laboratory settings assessments of attention control. Typically, in laboratory assessments of self-regulation of children and adolescents, frustration and rewards are studied that are out of the context of close relationships with caregivers and peers. Very low correlations have been found between the key evoked response potential (ERP) indices of self-regulation and behavioral measures of self-regulation. Most surprising has been the lack of correlation between parent and youth report of effortful control or executive functioning on either ERP or behavior measures of self-regulation in laboratory settings (Felver, Dishion, & Racer, in preparation). However, under conditions of fMRI anterior cingulate activity has been detected in response to Posner's attention network task (ANT), and chronic adolescent drug users showed more activation than did controls (Abullaev, Posner, Nunnally, & Dishion, 2010). Moreover, when adolescents were placed in a driving task scenario in which peer attention was manipulated, in general they were shown to engage in higher risk driving behavior (Peake, Dishion, Stormshak, Moore, & Pfeifer, 2013).

Thus there is considerable evidence that individual differences in self-regulation in children and adolescents are prognostic of various forms of problem behavior at both developmental phases. Seriously needed is a multilevel program of research that addresses the challenges of measurement problems and the lack of convergence of key indicators of self-regulation measured at the level of global ratings, electrophysiology, and neuroimaging, and at the behavioral level. From this work one may expect that the child's challenges in managing behavior under

conditions of reward will emerge as a key vulnerability factor. Identifying the relative magnitude of genetic and environmental effects at various ages and developmental periods will be especially helpful for the design of effective prevention strategies that apply to an array of public health outcomes, from violence to drug abuse.

Linking Theory to Intervention

The study of antisocial behavior in children and adolescents is often a very applied effort. The applied focus of this area of research is centered on the need to develop improved interventions that address the multiple needs of these vulnerable and potentially dangerous children and adolescents. A simple perusal of evidence-based literature reveals several intervention strategies for antisocial behavior that are effective in childhood (Webster-Stratton & Reid, 2010; Zisser & Eyberg, 2010), middle childhood (Forgatch & Patterson, 2010; Kazdin, 2010; Sanders & Murphy-Brennan, 2010), and adolescence (Henggeler & Schaeffer, 2010; Liddle, 2010; Smith & Chamberlain, 2010; Waldron & Brody, 2010). Thus, the applied program of research has been quite successful.

A summary of the effective strategies suggests that two components are especially important to successful interventions: (1) support to caregivers with respect to motivation and to behavior management skills; and (2) support to youths for developing self-regulatory skills associated with antisocial behavior. In the past 10 years considerable progress has been made in applying the principles of evidence-based intervention to changing entire communities. For example, Forgatch and colleagues collaborated with researchers in Norway and successfully implemented PMTO, and found that generations of therapists were able to achieve the same effects as those of the program developers (Ogden et al., 2012). There is also evidence that principles of behavior change can be applied to entire communities to reduce the prevalence of problem behavior. For example, the pioneering work of Hawkins and colleagues randomly assigned communities to a support system called Communities That Care and found significant effects on children's antisocial behavior (Hawkins, Catalano, & Kuklinski, 2012). Other researchers have shown that a universal approach to promoting evidence-based parenting practices can reduce the incidence of child abuse in communities (Shapiro, Prinz, & Sanders, 2010). Science points the way to reduce the incidence and prevalence of these problem behaviors at the community level, but it is troubling to note that willingness to allocate the necessary resources and training to accomplish this goal seems limited.

Unfortunately, publishing successful interventions and neglecting null or negative findings is the rule rather than the exception. Given the state of funding for intensive longitudinal studies, it becomes possible to selectively ignore measures that are not sensitive to change while attending to others that show intervention effects. At times comparing those variables that show effects with those that do not can provide insights about the complexity of the developmental phenomenon being targeted (Eddy, Dishion, & Stoolmiller, 1998). Other times, we may surmise that measures that do not show intervention effects are simply poor measurements (see Meehl, 1978, for an extended discussion).

The cascade model shown in Figure 15.1 that is supported by several longitudinal studies has implications for intervention theory with respect to the timing and type of intervention needed to improve the lives of children and adolescents with antisocial behavior. I suggest that our intervention science is half full, in that we have shown we can reduce many forms of antisocial and problem behavior at various stages of development. However, we have been less successful in showing that we can return youths to adaptive functioning in other areas that are essential for normative development and well-being. Figure 15.15 provides a summary of the two sides of the developmental cascade. When focusing on problem development, we see

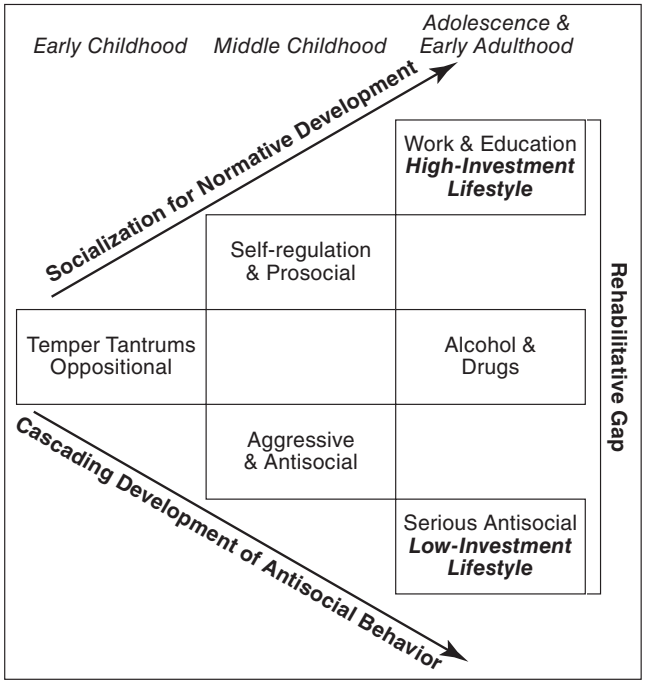


Figure 15.15 Normative and antisocial development and young adult rehabilitation.

that children can cascade into increasingly problematic behavior patterns and environments entrenched with support for deviance. However, on the positive side, caregivers are able to support the development of self-regulation and prosocial behavior from childhood through adolescence. The development of this complex array of abilities enables many, and indeed, most, to walk the same high-risk settings and not engage in the problem behavior or drug use they see around them. There is no temptation, because the behaviors are so clearly a distraction from more important and salient long-term goals. Without doubt, time of onset of the problem behavior affects both positive and negative child adjustment outcomes. Thus adolescence-onset youths more likely have a modicum of self-regulation, especially in specific domains in which they have had practice and support (e.g., finishing homework assignments, working quietly and focusing, taking turns in social interaction). Understanding that development of self-regulation is generally improving and problem behavior is decreasing allows us to rethink the intervention needs of early- versus late-onset adolescents.

Interventions designed to treat adolescents with a long history of problem behavior, including ADU, may require provision of more intensive support for inhibiting the behavior and for successful prosocial engagement and development of self-regulation skills (Figure 15.15). The disparity between prosocial and problem behavior may be referred to as a *rehabilitative gap*. In many ways models such as the teaching-family model are on the right track in that they are used to reduce problem behavior in the treatment home and improve academic skills. The shortcoming is that these improvements may not be maintained if the youths are returned to an environment that is replete with opportunities for problem behavior. We may have underestimated the needs of these vulnerable youths and the plasticity of their behavior in response to positive and negative social environments. In contrast, youths with a relatively positive developmental history who become drug involved in adolescence may require less in the way of support for prosocial development and more attention to the immediate self-regulatory demands associated with ADU. Identifying the optimal intervention strategy that meets the specific needs of children and adolescents is the cornerstone of the FCU's adaptive and tailored approach (Dishion & Kavanagh, 2003; Dishion & Stormshak, 2007). However, for youths who initiate antisocial behavior early, this approach has been less successful in terms of prevention and treatment; for example, my research group found it to be ineffective for reducing arrests and violence (Connell, Klostermann, & Dishion, 2012; Van Ryzin & Dishion, 2012). On the other hand, for adolescents who initiated delinquent behavior late, the number of court contacts was reduced. As shown in the model in Figure 15.14, highest risk youths might be better served in an adaptive, tailored framework that assesses both caregiver parenting and youth prosocial development and self-regulation, after which interventions target those specific needs.

At this juncture, two comments and one suggestion for future directions must be made. First, ample evidence for a developmental cascade process seems to account for amplification of deviance over time (Dishion et al., 2010; Dodge et al., 2008). Doubtless, some violent offenders act alone and are not directly supported by a peer group. Although many school shootings, for example, have elements of group support and contention as a preamble to violence, many individual violent and aggressive acts appear to be an outcome of individual rumination that has no clear history in the individual aside from acquisition of a weapon and ammunition. Data suggest that if interventions addressed and reduced the developmental processes described in this chapter, then a significant level of violence in many communities could be curtailed and even prevented.

Second, some interventions are not yet effectively addressing the peer group dynamics seemingly left to run amuck in urban communities immobilized by poverty, joblessness, and marginalization of some of our fellow citizens (Sampsom & Laub, 1994). A historical perspective confirms that problems of gangs and gang violence are not isolated to a specific group of people defined by culture, religion, or race. The process of marginalization is an ever-shifting target that changes across eras and geographic boundaries. Self-organization into peer groups that promote violence is adaptive behavior, and as we know, extremely difficult to change once it is in place (Klein, 2006). This unique vantage point on the problem of peer group influence clarifies the role of status and hierarchy in generating problem behaviors. As has been discussed in this chapter, the need for status may breed some forms of aggression, and interventions that target aggression and bullying may either ignore this dynamic or inadvertently exacerbate youths' tendency to bully for status. At a developmental level, we need to address the process early, which likely begins with bullying and aggression as it unfolds in public school and in some neighborhood settings. Recent efforts to prevent bullying have come down to adults being reminded that it is unacceptable for youths to be unsafe and victimized in schools and public settings (Olweus, 1993). Effective prevention programs mobilize adults to

nurture, safeguard, and teach skills to youths to reduce bullying and aggression.

As is clear from the vast majority of the work described in this chapter, researchers' focus to date has been on the dark side of family and peer relationships. Normative and prosocial family development and peer relationships ordinarily do not get the attention of prevention and intervention researchers. However, all children have the potential to be either a kind person or violent. Would an effort to promote prosocial behavior, compassion, empathy, and self-regulation add significantly to the impressive array of interventions now available to reduce the dark side of family and peer relationships? Without doubt, the kinds of friendships and romantic relationships that emerge from a developmental history of antisocial behavior and violence are not happy and satisfying, and as such, provide very little reinforcement for kindness and compassion. A focus on health promotion may in fact have a unique bearing on the developmental cascade toward violence, and therefore is decidedly worthy of future research.

This is an exciting time for the behavioral sciences as the findings from unique methodologies converge on an increasingly clear picture of developmental trajectories leading to various forms of problem behavior in children and adolescents, as well as comorbidities. We are able to map the microsocial patterns that give rise to these outcomes and understand how such patterns influence the macrolevel dynamics associated with establishing peer networks and shopping for rewarding settings and opportunities that potentiate further maladaptation. At this juncture we must continue the mapping process of linking changes in neural circuitry with these micro and macrolevel changes, in the context of interventions designed to prevent and treat problem behavior.

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CHAPTER 16

Narcissism

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INTRODUCTION

The mythological figure Narcissus was a handsome, self-absorbed, and vain young man who passionately fell in love with his own reflection in the water. Although some degree of self-love may be healthy from time to time, Narcissus' self-love was obsessive. He ultimately pined away by the waterside, unable to let go of the reflection of himself that he loved so passionately. What Narcissus did not know at the time is that his personality would attract attention long after his death. Over the past century, psychologists and psychiatrists have had a vested interest in narcissism—the personality type, named after Narcissus, which is marked by a sense of grandiosity, and a strong need to get attention and admiration from others. In recent years, psychologists and psychiatrists have become increasingly interested in narcissism in youth. Considerable progress has been made in understanding how narcissism manifests in childhood and adolescence, how narcissism may emerge and develop over time, and how narcissism impacts youths' lives.

Narcissism lies at the intersection of normal and abnormal development: Typically developing youth gradually differ from one another in how narcissistic they are, and at the same time, higher levels of narcissism often (but not always) interfere with healthy psychological development. As such, our understanding of youth narcissism is likely to benefit from a developmental psychopathology approach: an integrative, interdisciplinary approach that seeks to elucidate both normal and abnormal narcissistic

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development over the life course. We hope that this chapter will encourage more developmental psychopathologists interested in personality and self-development to join the collaborative study of youth narcissism.

The goal of this chapter is to provide an integrative review of current knowledge of narcissism in children and adolescents. Despite the recent growth of interest in youth narcissism, one factor that hampers scientific progress is a lack of integration between disciplines, especially between developmental, social-personality, and clinical disciplines. Developmental and social-personality psychologists have typically conceptualized narcissism as a normal trait, an individual difference variable that is normally distributed in the general population. Clinical psychologists and psychiatrists, on the other hand, have often focused on narcissistic pathology, including the diagnostic category of narcissistic personality disorder (NPD). Because these different research approaches have remained largely separated thus far, little is known about how (if at all) the nature and development of trait narcissism and narcissistic pathology are different from one another. Most experts believe that the difference is dimensional, and that narcissistic pathology is an extreme manifestation of trait narcissism that is associated with more substantial impairment. This same assumption underlies the current chapter, but we note at the outset that more needs to be learned about how trait narcissism and narcissistic pathology are different. This chapter aims to integrate knowledge from different disciplines into a comprehensive understanding of youth narcissism, addressing both its normal and its pathological manifestations.

We begin by discussing historical conceptions of narcissism. Although the term narcissism was coined by the end of the nineteenth century, philosophers have been discussing the topic of self-love for ages. What these writings teach us is that grandiose and entitled self-views have been a source of intellectual curiosity and concern throughout history. We then consider the manifestations of trait narcissism and narcissistic pathology. Narcissism has both grandiose manifestations (such as inflated feelings of superiority and entitlement) and more vulnerable manifestations (such as sensitivity to negative interpersonal evaluation). Although there is a common core of narcissistic characteristics that presumably can be found in narcissistic individuals of all ages, some narcissistic characteristics appear to be more typical in youth than in adults. Next, we address common questions and concerns regarding the assessment of youth narcissism. Narcissistic traits in youth are best measured using self-report instruments, and at least two psychometrically sound self-report instruments are now available to measure trait narcissism in older children and adolescents. We also discuss key theoretical models of narcissism, stemming from the social-personality and clinical literature. These models help understand how seemingly paradoxical narcissistic characteristics are interrelated, and why narcissistic maladjustment often persists over time. We then address the etiology and development of narcissism, focusing on when and why narcissism may emerge. We cast narcissism as a derailment of normal self-development, and propose a diathesis–stress model for the developmental origins of narcissism. Next, we discuss clinical and applied issues, such as why clinicians may or may not want to diagnose NPD in youth, how narcissistic pathology is different from closely related forms of pathology, and how we can intervene with narcissism and its consequences. Finally, we address three key controversies that surround the topic of youth narcissism—whether or not narcissism has been on the rise over the past decades, whether or not narcissism is partially adaptive, and whether or not narcissists hold deep-seated feelings of insecurity and inferiority. Thus, this chapter comprehensively reviews current knowledge of youth narcissism, and calls into attention the many exciting opportunities to further uncover the developmental psychopathology of narcissism.

HISTORY OF NARCISSISM

The myth of Narcissus can be traced back to the Thracians (a group of Indo-European tribes living in the fifth and fourth century BC; Wieseler, 1856), and entered into Western literature through Ovid's poems. Narcissus was born to the nymph Liriope. From his birth on, Narcissus was admired for his beauty. When a prophet was asked whether Narcissus would live to ripe old age, he answered: "Unless he knows himself." Narcissus grew up surrounded by people who admired his beauty, but at the same time, he turned down the overtures of those who admired him. Eventually, the pain Narcissus had caused to others was punished by goddess Nemesis, who condemned him into unrequited love—"So may he love himself, and not get what he loves!" One day, Narcissus lay down by a pool and caught a glimpse of himself in the water. Paralyzed by the beauty of his own image, Narcissus failed to eat and sleep, and slowly pined away at the waterside. He turned into a flower with white leaves and a saffron center, bowing down to the water.

The concept of Narcissism has had many different definitions and connotations since it was introduced

in the psychological literature. We first describe what philosophers and other thinkers wrote about self-love and narcissism. Then, we describe the multiple meanings that narcissism has had in psychology, and we outline two lessons that the history of narcissism has taught us.

Self-Love in Philosophy

The topic of self-love has fascinated philosophers from ancient times onward, long before narcissism was studied by psychologists. Schools of thought differed in how they defined self-love. Broadly, there have been three philosophical definitions of self-love—self-love as self-enhancement, self-love as self-preservation, and self-love as self-maximization.

Self-Love as Self-Enhancement

Conventional wisdom often refers to self-love as the tendency to place much worth on oneself as a person, while being blind to one's failures or inadequacies. This conceptualization of self-love already appears in ancient philosophy. Several pre-Christian Greek philosophers considered such self-love to be a universal human trait. For example, Plato (trans. 2008) believed that "men are not in the habit of dwelling upon the dark side of their own lives. . . . They are very kind and very blind to their own faults; the rhetoric of self-love is always pleading with them on their own behalf" (p. 40). Although some degree of self-love was considered universal, philosophers recognized that there are individual differences in self-love as well. For example, in his book *The Characters*, Theophrastus (a student of Aristotle) described 30 moral types, including the boastful man: "The Boastful Man will stand in the market at the Piraeus and tell foreigners that he has a good deal of money invested at sea; . . . and while he is exaggerating this beyond all proportion he will send his slave to the bank, although there is [not even a single] drachma in his account" (Theophrastus, 2004, p. 131).

Much like narcissists, the boastful man exaggerates his talents and achievements and tries to instill upon others an overly positive image of himself. Later philosophers have proposed that self-love may give rise to defensiveness and hostility. For example, French philosopher Pascal (1829) noted: "But to what a state is man reduced! He cannot prevent this object of love from being full of defects and miseries" (p. 71). "This state of disappointment," Pascal argued, "generates in [man] the most wretched and criminal passion that can be imagined: he conceives a deadly hatred against the truth which reproves him, and convinces him of his faults" (p. 71). Similarly, La Rochefoucauld (1658/1851) believed that "[self-love] makes men idolize themselves, and would make them tyrants over others if fortune were to give them the means" (p. 1).

Self-Love as Self-Preservation

Stoics, such as Chrysippus, referred to self-love as a universal tendency of humans to secure their own survival. Self-love was seen as an innate tendency to promote self-preservation. As Diogenes Laertius (trans. 1853) summarized the Stoic view, "[We] must assert that nature has bound the animal to itself by the greatest unanimity and affection; for by that means it repels all that is injurious, and attracts all that is akin to it and desirable" (p. 290). Among later philosophers, Voltaire (1764/1856) similarly believed that "self-love is the instrument of our preservation; it resembles the provision for the perpetuity of mankind" (p. 297).

Self-Love as Self-Maximization

Another philosophical tradition considered self-love a tendency to maximize oneself, either by striving for noble qualities (e.g., seeking to do noble deeds), or by striving for hedonism (e.g., seeking bodily pleasures).

Aristotle (trans. 1984) distinguished between self-love of "good" and "wicked" people (p. 1847, 1919). Good people's self-love is expressed when they assign to themselves noble qualities, and try to act in accordance with these qualities. By doing noble deeds, good people benefit not only others but themselves as well, such as through the interpersonal approval that noble deeds yield. Such self-love also underlies true friendship, Aristotle argued: because people tend to experience friends as part of the self, good people love their friends as they love themselves (p. 1843). In contrast, wicked people's self-love is expressed when they "assign to themselves the greater share of wealth, honours, and bodily pleasures" (p. 1847). According to Aristotle, wicked people are greedy and excessively focused on gratifying their own needs, while disregarding the needs of others.

French philosopher Rousseau (1762/1979) also proposed two forms of self-love, *amour de soi* and *amour-propre*. He proposed that children are born into a state of *amour de soi*, or healthy self-love. "A child's first sentiment is to love himself; and the second, which derives from the first, is to love those who come near him" (p. 213). Throughout development, however, children's healthy self-love is corrupted by society, and may give rise to *amour-propre,* which is a "relative sentiment, artificial and born in society, which inclines each individual to have a greater esteem for himself than for anyone else,

inspires in men all the harm they do to one another" (Rousseau, 1755/1993, p. 91). *Amour-propre* leads children to compare themselves with others, to place excessive value on themselves, to expect admiration from others, and to feel entitled—in fact, what Rousseau labeled *amour-propre* shares much similarity to what we define as narcissism today.

Similarly, English philosopher Joseph Butler distinguished between *cool self-love* and *sensual self-love*. Cool self-love refers to a desire for obtaining happiness, and thus motivates behaviors that promote happiness. Much like Aristotle and Rousseau, Butler (1726/1828, p. 27) argued that self-love and benevolence are "so perfectly coincident . . . that we can scarce promote one without the other." In his view, "self-love is one chief security of our right behaviour towards society" (p. 27). Similarly, Voltaire argued that people should embrace rather than reject their self-love, because "it is love of self that encourages love of others, it is through our mutual needs that we are useful to the human race" (as cited in Hulliung, 2001, p. 63). In contrast, sensual self-love refers to a desire for obtaining sensual pleasure, such as obtaining pride, power, and bodily pleasures.

Summary

The topic of self-love has been of focal interest to philosophers for a long time. Strikingly, ancient philosophers already distinguished between healthy and unhealthy forms of self-love, foretelling, in a sense, current empirically based attempts to distinguish healthy and unhealthy forms of favorable self-regard (e.g., Thomaes, Brummelman, Reijntjes, & Bushman, 2013). Some forms of self-love were assumed to foster self-preservation, compassion, and the ability to form close relationships. Other forms of self-love were assumed to foster entitlement, egoism, greed, and a need for admiration. It is the latter form of self-love that most closely resembles our current conceptions of what narcissism entails.

Narcissism as Sexual Disorder

Although philosophers had discussed the topic of self-love for centuries, it was not until the end of the nineteenth century that the term narcissism was introduced to psychology. British physician and sexologist Havelock Ellis (1898) was the first to use the mythical figure Narcissus to describe psychological phenomena. In his clinical practice, he encountered people who—much like Narcissus—found much pleasure, even erotic pleasure, in gazing at themselves in the mirror. He considered these people Narcissus-like. One of his Narcissus-like patients was a 28-year-old woman:

> She is a handsome woman, of very large and fine proportions. . . . She has an intense admiration for her own person, especially her limbs; she is never so happy as when alone and naked in her own bedroom, and, so far as possible, she cultivates nakedness. She knows by heart the various measurements of her body, is proud of the fact that they are strictly in accordance with the canons of proportion, and she laughs proudly at the thought that her thigh is larger than many a woman's waist. (Ellis, 1927/2007, pp. 188–189).

Yet, Ellis did not coin the term *narcissism*. German psychiatrist Näcke (1899) wrote a summary of Ellis's work and first used the term narcissism (*Narcismus*) to refer to the sexual condition in which people view their own body as a sexual object.

Narcissism as Developmental Phase

In the early twentieth century, psychoanalysts further elaborated upon the concept of narcissism. During this period, narcissism gradually became detached from its initial meaning as sexual disorder. Psychoanalysts such as Sadger (1908), Freud (1910), and Rank (1912) proposed that narcissism—which they defined as love for the self—is a normative developmental phase, which children pass through for healthy development. Consistent with the idea of narcissism as normative phase, Freud highlighted several narcissistic traits of young children—including their overly positive self-views, their egocentrism, their illusions of power, and their belief in the magic powers of their thoughts and wishes.

In his paper *On Narcissism*, Freud (1914/1957) proposed that narcissism reflects libido invested in the self, which comes at the cost of libido invested in others. Thus, controversially, Freud suggested that the more people love themselves, the less they love others. Freud also argued that children are born in a state of *primary narcissism*, in which their libido is still entirely directed toward the self, not toward others. In normal development, he argued, children proceed from self-love to other-love and gradually come to direct their libido toward others. Even though Freud thought of narcissism as a developmental phase that children normally leave behind, he also believed that some relics of early narcissism remain apparent throughout life. For example, he noted that "if we look at the attitude of affectionate parents toward their children, we have to recognize that it is a revival and reproduction of their own narcissism, which they have long since abandoned" (Freud, 1914/1957, pp. 90–91).

Thus, early psychoanalysts considered narcissism a normative developmental phase in early childhood. This view has never been empirically confirmed, however, and so it has disappeared from current conceptualizations of narcissism. Later theorizing paved the way for the current view of narcissism as a personality trait rather than a sexual disorder or developmental phase.

Narcissism as Personality Trait

Adult Narcissism

Jones (1913/1951) was the first to describe narcissism as a personality trait. He identified the so-called *God Complex*, a term he used to describe the unconscious fantasy that some people may hold of identifying themselves with God. "The main foundation of the complex," Jones believed, "is to be discovered in a colossal *narcissism*" (p. 247). According to Jones, people with the God Complex are self-effacing, aloof, inaccessible, and unsocial. They are not shy or inhibited, but rather feel superior to other people and therefore feel the need to disengage from them. They fantasize about having power over others, and believe they are omniscient.

Sometime later, Wälder (1925) wrote that people with narcissistic personalities feel superior to others and are self-focused, preoccupied with admiration, and in lack of empathy. Subsequently, Freud (1931/1961) wrote a paper on so-called libidinal types, which he described as normally distributed basic personality traits, which included the narcissistic type:

> The subject's main interest is directed to self-preservation; he is independent and not open to intimidation. His ego has a large amount of aggressiveness at its disposal, which also manifests itself in readiness for activity. . . . People belonging to this type impress others as being 'personalities'; they are especially suited to act as a support for others, to take on the role of leaders and to give a fresh stimulus to cultural development or to damage the established state of affairs. (P. 218).

Wilhelm Reich (1933/1972) proposed in his book *Character Analysis* the phallic-narcissistic character. According to Reich, phallic-narcissistic individuals feel superior to others, and are overly confident, arrogant, haughty, and provocative or even sadistic in their relationships. Reich described these individuals' tendency to lash out aggressively when their egos are threatened. "If their vanity is offended, they react with cold disdain, marked ill-humor, or downright aggression" (p. 218). Reich believed that phallic-narcissism, perhaps unsurprisingly given the term, originates from "an identification between the ego as a whole and the phallus" (p. 219).

An important contribution was made by Horney (1939), who distinguished narcissism from self-esteem. In her view, narcissism represents *unrealistic* self-inflation (i.e., valuing oneself for characteristics and values that one does not possess in reality), whereas self-esteem represents *realistic* self-evaluation (i.e., valuing oneself for characteristics and values that one does possess). Thus, whereas other theorists believed that the difference between narcissism and self-esteem was only quantitative (i.e., with narcissism representing extremely high self-esteem), Horney believed that narcissism and self-esteem were qualitatively different.

Additionally, Horney disagreed with the popular idea in her time that narcissists simply love themselves too much. Instead, she believed that narcissism is "an expression not of self-love but of alienation from the self" (Horney, 1939, p. 99–100). According to Horney, narcissists feel that to be accepted by others, they must be as others expect them to be. That is, their self-evaluations are overly contingent upon others' approval. "[The narcissistic child] is bad or stupid when others think he is bad or stupid, intelligent when others order him to be intelligent, a genius when others consider him one" (Horney, 1939, p. 92). Horney believed that narcissistic children attempt to escape painful feelings of self-alienation by conceiving of themselves as superior beings. Yet this thin veneer of self-love may easily give way to feelings of worthlessness when narcissists fail to obtain approval from others.

The notion that narcissism might be a defense against vulnerability inspired the thinking of subsequent theorists. For example, Annie Reich (1960) suggested that narcissists are unable to regulate their self-esteem in healthy ways, and often experience strong self-esteem fluctuations. She noted that narcissists' self-esteem can quickly rise to a sense of grandiosity and then fall deeply into self-despise. To defend themselves against negative self-feelings, narcissists retreat from others and turn their attention inwards, where the world is a better place: "It is not so. I am not helpless, bleeding, destroyed. On the contrary, I am bigger and better than anyone else. I am the greatest, the most grandiose" (Reich, 1960, p. 220).

Much like early psychoanalysts, Kohut (1971) cast narcissism as a normative developmental phase. He argued that children are born in a state of primary narcissism, which is then disturbed by inevitable shortcomings in parental care. In response, children establish two core aspects of the self: the so-called *grandiose self* and the *idealized parent image*. Under optimal developmental conditions, the grandiose self and the idealized parent image

become integrated into adult personality. The grandiose self comes to underlie individuals' ambitions, enjoyment, and self-esteem, and the idealized parent image comes to underlie individuals' ideals. However, so Kohut argued, if children experience trauma (e.g., when their parents are insensitive to their needs), the grandiose self and the idealized parent image may keep their original form and may lead to pathological narcissism. Thus, Kohut thought that pathological narcissism arises from developmental arrest, and is only quantitatively different from normal narcissism.

In contrast, Kernberg (1975) believed that pathological narcissism is qualitatively different from normal narcissism. In his view, normal narcissism arises from libidinal investment in self-representations that can be both positive and negative, and allow for realistic self-evaluation. By contrast, pathological narcissism arises from libidinal investment in self- and object-representations that can only be positive. In pathological narcissism, negative representations are repressed, dissociated, and projected onto the external world—giving rise to narcissists' negative views of others.

The works of Kohut and Kernberg on pathological narcissism have been influential in shaping our current understanding of NPD. In 1980, NPD was first introduced into the *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed. (*DSM-III*; American Psychiatric Association, 1980). It was included mainly because clinicians often identified narcissism in their patients but had no common ground for its diagnosis (Gunderson, Ronningstam, & Smith, 1995).

Taken together, multiple theorists and clinicians, especially psychoanalysts, have made contributions to the early understanding of narcissism as a form of personality. They described the intra- and interpersonal manifestations of adult narcissism, distinguished it from self-esteem, tried to understand its developmental roots, and identified healthy as well as unhealthy forms of narcissism—themes that are still of primary interest to empirical researchers today.

Youth Narcissism

From the 1980s, clinicians became increasingly interested in youth narcissism, and started studying narcissism in children and adolescents (for early examples, see Miller, 1981; Ornstein, 1981; Rinsley, 1980). These authors sought to answer questions regarding the diagnosis, treatment, and developmental origins of narcissistic pathology.

Rinsley (1980) and Bleiberg (1984) offered a developmental approach to diagnosing pathological narcissism in children. They argued that pathological narcissism results from children's failure to accomplish important self-developmental tasks. For example, Bleiberg (1984) argued that narcissistic children have often failed to achieve an autonomous identity, to relinquish feelings of omnipotence, to develop a sense of self-esteem that is independent of others' evaluations, to develop a resilient ego to cope with the stresses of life, or to internalize moral standards.

Kernberg (1989) described the characteristics of narcissism in childhood, and addressed how normal narcissism might differ from pathological narcissism. She argued that it is normative for young children to have grandiose fantasies, try to control their parents, try to be at the center of attention, and take pride in their accomplishments. What distinguishes children with pathological narcissism, she argued, is that these children use their grandiose fantasies to maintain emotional equilibrium, have a strong need to be admired by everyone, have unrealistic expectations of others, take pride in their accomplishments only to the extent that they capture others' attention, and are unable to show genuine love for others.

Bleiberg (1994) also discussed what may distinguish narcissistic development from more typical development. He proposed that *narcissistic vulnerability*—feelings of shame that arise from a discrepancy between one's ideal self and actual self—is central to both normal and pathological development, and is especially prominent during adolescence. According to Bleiberg, narcissistic vulnerability "provides one of the fundamental engines of growth throughout life" (p. 37) by motivating people to reach their ideals. In normative development, children do not experience extreme narcissistic vulnerability, because they have ideals that can realistically be met. What distinguishes narcissistic development, he argued, is that children have ideals that cannot realistically be met, as evident from narcissists' tendency to hold unrealistically positive, inflated self-views.

In summary, over the past 3 decades, clinical interest in youth narcissism has resulted in theoretical contributions to our understanding of its manifestations, developmental roots, and developmental consequences. Clinicians were the first to recognize that narcissism can be observed in children and adolescents.

Empirical Research on Narcissism

Until the 1980s, virtually all literature on narcissism was based on clinical observation rather than empirical data. The inclusion of NPD in the *DSM* in 1980 changed this trend, and encouraged empirical researchers to develop self-report instruments to measure narcissism in both

general population and clinical samples of adults. In 1979, Raskin and Hall (1979) developed the Narcissistic Personality Inventory (NPI), a self-report instrument that aimed to measure NPD traits as an index of subclinical narcissism (see Raskin & Terry, 1988, for the final version of the NPI). The NPI rapidly became the standard measure of trait narcissism, and sparked a strong increase in research on narcissism in adults. Empirically oriented clinical and social-personality psychologists started exploring the structure and correlates of narcissism, and how narcissism impacts psychological adjustment and interpersonal behavior. More recently, developmental psychologists started exploring the development, manifestations, and origins of narcissism in youth.

Conclusion

The concepts of self-love and narcissism have been studied for centuries. The history of narcissism teaches two important lessons. The first lesson is that research and practice benefit from a clear and strict definition of narcissism. Up to today, it is not unusual for researchers and practitioners to equate narcissism with traits such as self-esteem, egoism, and egocentrism—concepts that are clearly distinct from narcissism. The second lesson is that, while narcissism was already of interest to ancient philosophers, empirical research interest in narcissism has steeply increased over the past three decades. The development of standardized self-report measures to assess narcissism in adults (and, more recently, youth) was key to this development. Yet, there might be another factor that has accounted for increased interest in narcissism as well. Perhaps it is no coincidence that interest in narcissism rose over the exact same time period that Western society itself became more individualized, self-focused and, according to some, narcissistic (for a discussion, see *Controversies* section). Psychologists do not live in a social vacuum; they are influenced by the salient societal phenomena of their time.

NARCISSISM AND ITS MANIFESTATIONS

Most laypersons have at least some notion of what narcissism involves. When asked to describe a prototypical narcissist, they will often describe individuals who think remarkably highly of themselves, who seem to be constantly on the lookout to draw attention to themselves, who feel entitled to special privileges or exceptional treatment, who feel superior to others even when there is no obvious reason to do so, or who are arrogant and feel disdain for other people. Such depictions are correct: they all describe common features of narcissism. Yet these depictions do not tell the whole story: There is more about narcissism than common belief suggests. Indeed, narcissistic individuals also attach great importance to what others think of them, are emotionally sensitive to even the slightest of criticisms, feel easily rejected or ridiculed by others, quickly lose their feelings of grandeur, and feel ashamed or enraged as readily as they feel proud or enchanted. If anything, narcissists are individuals full of paradoxes.

Many of the aforementioned traits and behavioral dispositions can be found in adults as well as in youth. Indeed, most laypersons will be able to think of (older) children or adolescents they know who seem to hold inflated self-views, seek to place attention on themselves, and show haughty interpersonal attitudes. In this section, we first review current knowledge of the manifestations of trait narcissism and narcissistic pathology as derived from research involving adults. Next, we review emerging knowledge of how narcissism is manifest in children and adolescents.

Manifestations of Narcissism in Adults

Clinicians and researchers typically agree that the phenotypic manifestations of narcissism converge into two broad dimensions. These dimensions have received different labels, such as *thick-skinned* versus *thin-skinned*, *egotistical* versus *dissociative*, *oblivious* versus *hypervigilant*, *exhibitionistic* versus *closet*, and *grandiose* versus *vulnerable* narcissism (see Cain, Pincus, & Ansell, 2008, for an overview). It is the latter label of grandiose versus vulnerable narcissism that is now most commonly used (Dickinson & Pincus, 2003). We will use this same terminology in the present chapter as well.

Diagnostic Approaches

The *DSM-IV* (American Psychiatric Association, 2000) includes NPD as a personality disorder to be diagnosed using the following criteria: (1) grandiose sense of self-importance; (2) fantasies of unlimited success; (3) feelings of being special and unique; (4) requiring excessive admiration; (5) harboring a sense of entitlement; (6) being interpersonally exploitative; (7) lacking empathy; (8) being envious often; and (9) showing arrogant, haughty behaviors. As one may notice, these criteria mainly emphasize the grandiose, self-assured aspects of narcissism. Yet, in an accompanying paragraph, it is argued that "vulnerability in self-esteem makes individuals with NPD very sensitive to 'injury' from criticism or defeat. Although they

may not show it outwardly, criticism may haunt these individuals and may leave them feeling humiliated, degraded, hollow, and empty" (American Psychiatric Association, 2000, p. 715). Thus, according to conventional diagnostic guidelines, narcissistic pathology involves both grandiose and vulnerable traits.

Clinical Observations and Empirical Research

The differential manifestations of narcissistic pathology are acknowledged in clinical observations and empirical research as well (e.g., Akhtar & Thomson, 1982; Fossati et al., 2005; Ronningstam, 2009). For example, in reviewing clinicians' accounts of the manifestations of narcissistic pathology, Ronningstam (2009, p. 113) distinguished between what she called arrogant (i.e., grandiose) and inhibited, shame-ridden, and hypersensitive (i.e., vulnerable) manifestations:

> Outstanding for the arrogant type is the more striking predominant presentation, with openly featured expressions of self-serving and enhancing behaviors and attitudes in their more active and deliberate interactions with others. This is in contrast to the inhibited, shame-ridden, and hypersensitive shy type, whose low tolerance for attention from others and hypervigilant readiness for criticism or failure makes him/her more socially passive, tuned in, and interpersonally awaiting. Nevertheless, under a modest surface, the shy narcissistic individual is equally preoccupied with self-enhancing fantasies and strivings and hyperreactive to oversights or unfulfilled expectations from others.

Extending clinical observation, one empirical study (Russ, Shedler, Bradley, & Westen, 2008) asked a large random sample of psychiatrists and clinical psychologists to provide detailed descriptions of the patients they treated using a standardized protocol. The researchers used Q-factor analysis (a statistical technique that groups together individuals with similar traits) to be able to identify subtypes of NPD patients. Two substantial groups of patients emerged from this analysis: one group that the authors labeled grandiose/malignant (i.e., grandiose narcissists), and another group that they labeled fragile (i.e., vulnerable narcissists). Both groups of patients showed some similar traits—traits that might be viewed as the common core of NPD: Both groups of patients were described as having an exaggerated sense of self-importance, and holding an adversarial interpersonal orientation (i.e., they were prone to being hostile and critical of others). Still, there were several important differences in how NPD was manifest in the two groups. Grandiose narcissists were described by their therapists as holding a tendency to feel entitled and privileged, to manipulate others and seek power, and to lack empathy. Moreover, they were said to frequently get into power struggles, and to hold long-lasting grudges. By contrast, vulnerable narcissists were characterized by their therapists as being prone to experience negative affect (e.g., depressed or anxious affect, envy), to ruminate over negative events, and to be unable to maintain close relationships. Thus, this study provided empirical evidence that narcissistic pathology can take different forms.

Social-Personality Research

Social-personality research has mainly focused on trait narcissism, and also found compelling evidence for the distinction between grandiose and vulnerable manifestations of narcissism.

In an initial study, a principal-component analysis was conducted on a number of trait narcissism scales derived from the Minnesota Multiphasic Personality Inventory, which was completed by a community sample of adult participants (Wink, 1991). This analysis yielded two orthogonal factors, labeled grandiosity–exhibitionism (i.e., grandiose narcissism) and vulnerability–sensitivity (i.e., vulnerable narcissism). Although the two factors shared a common core of grandiose beliefs and disregard for the needs of other people, they were marked by distinct patterns of psychological and interpersonal adjustment. Grandiose narcissism was associated with self- and observer-ratings of extraversion, exhibitionism, self-assurance, and aggression; vulnerable narcissism was associated with introversion, anxiety, and defensiveness.

In another study (Rose, 2002), participants completed measures designed to assess subclinical traits of grandiose narcissism and vulnerable narcissism. Grandiose narcissism was positively associated with self-esteem, happiness, and life satisfaction. Conversely, vulnerable narcissism was negatively associated with these indices of well-being. Importantly, the links between narcissism and well-being were mediated by self-esteem, such that grandiose narcissists had higher well-being because they held high self-esteem, and vulnerable narcissists had lower well-being because they held lower self-esteem.

In a more recent study (Miller et al., 2011), participants completed a number of standard measures of trait narcissism, as well as measures of personality, interpersonal behavior, and psychopathology. The two factors that emerged from factor analysis were labeled grandiose and vulnerable narcissism. Both forms of narcissism were characterized by a disagreeable, antagonistic, and entitled interpersonal orientation. Yet grandiose narcissism

was associated more strongly with the Big Five trait of extraversion, and vulnerable narcissism was associated more strongly with the Big Five trait of neuroticism. Another major difference emerged in how both forms of narcissism were associated with cognitive-emotional schemas about interpersonal relationships. Whereas grandiose narcissism was not associated with attachment difficulties, vulnerable narcissism was associated with both anxious and avoidant attachment styles, suggestive of a fearful interpersonal orientation (involving fear for the loss of intimate relationships, and independence strivings at the cost of developing emotional closeness). Finally, grandiose and vulnerable narcissism differed in their associations with psychopathology. Vulnerable narcissism was linked to symptoms of internalizing pathology (depression and anxiety), as well as to symptoms of somatization, obsessive-compulsiveness, paranoia, and borderline and schizotypical personality. Grandiose narcissism was less clearly linked to symptoms of psychopathology, but did show robust links to antisocial traits.

Together, social-personality research on trait narcissism has used multiple research methods and measures of narcissism to find converging evidence that grandiose and vulnerable narcissism are distinctive manifestations of narcissism.

Two Cautionary Notes

In light of this evidence, it is tempting to think of narcissistic individuals as being either grandiose narcissists or vulnerable narcissists. In fact, in our own work, we have used such nomenclature as well (e.g., Thomaes, Bushman, Stegge, & Olthof, 2008). Although for clarity purposes it seems acceptable to cast grandiose and vulnerable narcissism as personality traits or subtypes that characterize certain individuals more than others, there is now emerging consensus that the different manifestations of narcissism are best conceptualized as *states* that oscillate or co-occur within the same individual (Pincus & Lukowitsky, 2010). Thus, at some times narcissistic individuals may be in a grandiose state, whereas at other times these same individuals may be in a more vulnerable state. In fact, such grandiose and vulnerable narcissistic states may alternate rapidly, such as when a narcissist feels on top of the world after being praised but feels like sinking into the ground after being criticized. To be sure, some narcissistic individuals may be more prone to exhibit grandiose characteristics, and others to exhibit vulnerable characteristics, but the notion that there are two types of narcissists is not entirely accurate.

Also note that the terms *overt narcissism* and *covert narcissism* are sometimes used as seemingly synonymous with *grandiose narcissism* and *vulnerable narcissism*, respectively. We agree with Pincus and Lukowitsky (2010), however, that it is best to use consistent terminology, and to refer to grandiose and vulnerable narcissism when describing the different phenotypes of narcissism. The terms overt and covert narcissism can be used to describe how these phenotypes are *expressed*. Some narcissistic characteristics are evident in observable behavior, such as narcissistic aggression, haughty interpersonal attitudes, or expressions of distress that follow from threatening events. These characteristics may be labeled overt narcissism. Other narcissistic characteristics are less observable patterns of cognition or emotion, such as fantasies of grandeur and superiority, or feelings of shame and humiliation that are held in check. These characteristics may be labeled covert narcissism. According to Pincus and Lukowitsky (2010), both grandiose and vulnerable narcissism can have overt and covert manifestations. Thus, overt and covert narcissism simply refer to how narcissistic phenotypes are expressed—they do not refer to narcissistic phenotypes themselves.

Manifestation of Narcissism in Children and Adolescents

There are various developmental factors (e.g., cognitive and emotional maturation, changes in age- and stage-relevant tasks) that are likely to influence how narcissism manifests among individuals of different ages.

In the following section, we will describe the main characteristics of narcissism in youth as evident from clinical observations and empirical data, focusing on those narcissistic characteristics that appear more typical in youth than in adults. In doing so, we follow the distinction between grandiose and vulnerable manifestations of narcissism.

Grandiose Narcissism: Clinical Observations

Phenotypic descriptions of grandiose narcissism from the clinical child and adolescent literature show considerable overlap with those from the clinical adult literature. In particular, feelings of superiority and entitlement, haughty and manipulative behaviors, and lack of genuine empathic concern for others have been described as core features of grandiose narcissism among youth, as much as they have been described as core features of grandiose narcissism among adults (e.g., Bleiberg, 1984; Kernberg et al., 2000). A few characteristics, however, stand out as typical manifestations of grandiose narcissism in children and adolescents.

First, grandiose fantasy has been described in clinical writings as one important means by which narcissistic

youth try to create and uphold their grandiose self-views, more than narcissistic adults do (Bardenstein, 2009; Bleiberg, 1984). Some common themes that narcissistic youth fantasize about are becoming wealthy, powerful, and physically attractive, or being capable of exceptional sports performances—or any other theme that allows them to feel they stand out from others. To be sure, especially in the early school years, it is not uncommon for typically developing children to engage in grandiose fantasy. What makes grandiose fantasy narcissistic is its age inappropriateness, its intensity, and the extent to which it interferes with children's daily functioning. For example, clinical observation suggests that grandiose fantasies tend to become less frequent from middle childhood in typically developing children, but not so in narcissistic children (Bleiberg, 1984). Some authors (Kernberg et al., 2000) have also argued that narcissistic fantasy differs from typical fantasy in the extent to which children believe that their fantasies reflect reality. Indeed, some narcissistic children do not just *fantasize* about being a superhero; they may actually believe they are a superhero. Such reality distortions may occur in children who suffer from more severe narcissistic pathology. Reality distortion by no means is a defining feature of narcissism: Many narcissistic children rationally understand that they are not superheroes, and may even realize that their personal traits or skills are not exceptional. Yet they cling to their grandiose fantasy because this makes them feel good about themselves.

Second, so-called false self-behavior (Harter, 2006, 2012) is a trait that is particularly salient among narcissistic youth, perhaps especially narcissistic adolescents (Bleiberg, 1984). False self-behavior refers to public acts that are discrepant with how one actually thinks or feels. Adolescents often feel that they are not acting in line with their true feelings, or that they behave in ways that someone else wants them to be (Harter 2006, 2012). In typically developing adolescents, false self-behavior often emerges as a form of role experimentation or in response to peer pressure. However, in narcissistic adolescents, false self-behavior is believed to result from a failure to develop an autonomous identity (Bleiberg, 1984) and from the intense desire to make positive impressions on peers. Because narcissistic adolescents may lack an authentic sense of who they are, and because they are highly motivated to obtain approval from peers, peer norms and expectations, rather than true feelings, may have a disproportionate impact on their behavior.

Third, age-inappropriate attitudes of self-sufficiency and self-reliance have also been described as typical for narcissistic youth (Bardenstein et al., 2000; Bleiberg, 1984). From a young age, many narcissistic children present themselves as not needing anyone, and being well able to take care of themselves. The common interpretation is that narcissists carefully avoid presenting themselves as in need of affiliation (even if the need for affiliation would be entirely age-appropriate), in an attempt to make themselves look independent or invulnerable. According to Kohut (1971), perhaps due to earlier experiences with parental coldness or abandonment, many narcissistic children lack trust that other people will support or care for them. To be able to cope with that painful belief, they may take a defensive interpersonal stance that communicates their self-reliance. Ironically, such a self-reliant interpersonal stance may cause even further detachment from others, potentially creating a downward spiral over time: Narcissists' detached interpersonal style might cause them to experience decreased interpersonal support, which may confirm them in the belief that other people are unlikely to support them, which subsequently cultivates their detached interpersonal style and ultimately may lead narcissists to become alienated from others. Illustratively, Bardenstein (2009) describes a young narcissistic client who noted that he had 1000 friends, but could not name anyone who knew him well or whom he trusted.

Grandiose Narcissism: Empirical Evidence

Empirical evidence on grandiose narcissism suggests considerable developmental consistency in the manifestations of narcissism. For example, research has shown that narcissistic children, much like older narcissistic individuals, tend to feel superior to others (Thomaes, Stegge, et al., 2008), and to hold more agentic than communal social goals (i.e., they are invested with establishing dominance and gaining respect from others, rather than with establishing close relationships; Thomaes, Stegge, et al., 2008).

One study examined adolescents' behavior on social networking sites, and found evidence suggesting that narcissistic adolescents are relatively concerned about making favorable impressions on others (Ong et al., 2011). In particular, narcissistic adolescents rated the pictures they posted on their Facebook profiles as more physically attractive, more fashionable, more glamorous, and more cool than less narcissistic participants did. Moreover, narcissistic participants updated their status on Facebook more frequently than less narcissistic participants, suggesting that they are eager to present to others what's on their minds. Importantly, these findings held even after controlling for extraversion, a personality trait that is associated with narcissism and also has strong impact on self-presentation.

Narcissistic youth are also prone to behave aggressively. In our own work, we have found that narcissistic children and adolescents can be particularly aggressive when they are faced with ego threatening experiences, such as when they are humiliated or ridiculed, criticised, or experience failure (Thomaes, Brummelman, Reijntjes, et al., 2013; Thomaes, Bushman, Orobio de Castro, Cohen, & Denissen, 2009; Thomaes, Stegge, Olthof, Bushman, & Nezlek, 2011). In one experimental study (Thomaes, Bushman, et al., 2008), participants (aged 10–13 years) first completed a measure of narcissistic traits and then played a competitive game with an unknown virtual opponent. The game was rigged so that participants lost. In the ego threat condition, participants were told their opponent was really bad on the task and that they should easily win. After losing, they saw their own name at the bottom of a ranking list on a bogus web page. In the control condition, they were told nothing about their opponent and did not see any rankings. Next, participants could blast their opponent with loud noise through headphones (a validated laboratory measure of aggression). Narcissists were more aggressive than others, but only when faced with ego threat. In fact, most aggressive were narcissists who had also reported very high self-esteem; narcissists who reported lower levels of self-esteem (potentially reflective of more vulnerable narcissism) were not more aggressive than other children. When triggered by ego threatening experiences, aggression is a manifestation of grandiose narcissism, in that it reflects an attempt to turn the tables and protect one's favorable self-image by restoring interpersonal dominance relations.

In addition to experimental findings, findings from survey research have consistently shown links between narcissism and predispositions to engage in physical, verbal, and relational aggression (i.e., excluding others, spreading rumors; Ang & Raine, 2009; Fossati, Borroni, Eisenberg, & Maffei, 2010; Golmaryami & Barry, 2010; Thomaes et al., 2009), aggression on the Internet (Ang, Ong, Lim, & Lim, 2010), and more broadly defined disruptive, antisocial, or delinquent behaviors (including stealing and lying; Barry, Frick, & Killian, 2003; Barry, Grafeman, Adler, & Pickard, 2007; Ha, Petersen, & Sharp, 2008). These findings were obtained in children and adolescents from both community and at risk samples, using different operationalizations of conduct problems, which attests to the robustness of the link between narcissism and conduct problems. Moreover, longitudinal research has found that narcissism also promotes the stability of aggressive behavior, such that aggressive young adolescents are more likely to remain aggressive over a 1-year period to the extent that they are more narcissistic (Bukowski, Schwartzman, Santo, Bagwell, & Adams, 2009).

Thus, there is rather comprehensive evidence for grandiose manifestations of narcissism among children and adolescents. The available literature, both clinical writings and empirical research, converges in suggesting that the grandiose manifestations of youth narcissism are in important ways similar to those in adults. Still, some manifestations are more salient in children and adolescents than they are at later age, including grandiose fantasy, false self-behavior, and age-inappropriate attitudes of self-sufficiency and self-reliance.

Vulnerable Narcissism: Clinical Observations

Phenotypic descriptions of vulnerable narcissism from the clinical child and adolescent literature show substantial overlap with those from the adult literature as well. Youth with narcissistic pathology are described to be hypersensitive to insults or criticisms, to feel unworthy when they fail to obtain admiration from others, to suffer from intense, recurrent feelings of shame and humiliation, and to be vulnerable to develop symptoms of anxiety and depression. A few characteristics stand out from clinical writings as early manifestations of vulnerable narcissism, manifestations that are less common or salient in adults.

Envy has been described as a manifestation of vulnerable narcissism that is relatively salient in children and, perhaps, adolescents. Narcissistic youth need reassurance that they are special, and accordingly, they tend to be hypervigilant to cues that other people get the attention and respect that they themselves seek to get (Bardenstein, 2009; Kernberg et al., 2000). They often avoid being a spectator of other people's accomplishments, deny that other people have exceptional skills, lead attention of audiences away from other people and direct it towards themselves, or express distress or resentment over other people's successes and opportunities. It is not uncommon for narcissistic children to be hostile to those who they see as attracting the attention that they themselves deserve to get. Narcissists tend to experience their quest for external validation as a zero-sum game, such that when other people gain attention or admiration, they believe this comes at the cost of their own chances to validate their grandiose egos: When other people stand out, narcissists feel unable to stand out themselves. Accordingly, envy can be considered a manifestation of vulnerable narcissism in that it is rooted in emotions of anxiety or distress over not being able to have one's grandiosity needs fulfilled. To be sure, adult narcissists are prone to experiencing envy as well, but they

may be better able to regulate their envy or to express it in more subtle ways.

Another salient manifestation of vulnerable narcissism in youth, especially adolescents, is the emotion of shame. Shame is the painful feeling associated with appearing worthless or inferior in the eyes of other people. Narcissistic youth are prone to experiencing shame for several reasons; they hold high standards for themselves (they want to radiate an image of perfection), and they are highly concerned about what other people might think of them. Consequently, when narcissists believe that others might see imperfections in them, they experience intense feelings of shame (Beren, 1988; Bleiberg, 1984). Normative developments in adolescence (e.g., increased self-consciousness, increased perceived importance of peer evaluation) already make shame a more common and painful emotion among typically developing adolescents. This normative development is magnified, however, among narcissistic adolescents, causing them to experience shame as particularly aversive. Importantly, precisely because shame is so painful, narcissists may sometimes try to repress or trump shame by less self-threatening forms of negative emotion, especially anger (Thomaes et al., 2011). Such an emotional state of shame-based anger has been called humiliated fury (Lewis, 1971).

Vulnerable Narcissism: Empirical Evidence

Empirical research has identified some manifestations of vulnerable narcissism in children and adolescents. First, correlational research found that narcissistic children are not only prone to experiencing positive affect, but to experiencing negative affect as well (Thomaes, Stegge, et al., 2008). If anything, narcissistic youth show emotional extremity, with episodes of positive affect (e.g., pride, euphoria) being interspersed with episodes of more negative affect (e.g., shame, dysphoria) relatively frequently. In one experiment, we found that public failure on an easy task causes children high in narcissistic traits to experience relatively intense feelings of shame, presumably because such failure threatens narcissists' grandiose self-image (Thomaes et al., 2011). Another experiment, conducted in a sample of adolescents, found that blatant positive feedback (participants were told, "You did much better than other people your age—great job!" following a general knowledge quiz) can sometimes cause vulnerable narcissists to feel shame, perhaps because they do not believe that such positive feedback is genuine (Malkin, Barry, & Zeigler-Hill, 2011; note that even in nonnarcissists, positive feedback is sometimes experienced as debilitating or discouraging (Brummelman, Thomaes, Orobio de Castro, Overbeek, & Bushman, 2014; Kamins & Dweck, 1999; Meyer, 1992). Thus, although more research is needed to identify situational triggers and boundary conditions, it is clear that narcissistic youth are prone to experience emotional extremity.

Similarly, we have found empirical evidence for the view that narcissists' self-esteem is vulnerable, and that they are prone to lose self-esteem following ego threatening events. In an experimental study (Thomaes et al., 2010), participants (aged 8–12 years) first completed a measure of narcissistic traits and then competed in an online popularity game, in which the least liked person was voted out of the group by a panel of peer judges. Participants first completed a personal profile (e.g., "How do you describe yourself?"). Next, participants in the social threat condition received negative feedback on their personal profile (they were announced as least likeable), whereas participants in the control condition received neutral feedback (an opponent was announced as least likeable). Both before and after the game, participants completed a measure of state self-esteem (e.g., I am satisfied with myself right now). Although most children lost some level of self-esteem following negative feedback, this effect was considerably stronger among narcissistic children: Narcissists tend to feel good about themselves, but they lose worth quickly in the face of negative social experiences.

Other empirical research has shown that narcissistic children and adolescents are prone to experience anxiety. Initial research found that narcissists are prone to experience symptoms of social anxiety, especially fear of negative evaluation (Thomaes, Stegge, et al., 2008). Thus, narcissistic youth are not only observed by clinicians to be socially anxious, they actually acknowledge and report being socially anxious as well. Other research has suggested that the anxiety problems of narcissistic youth may not be limited to social anxiety alone. Research among both children and adolescents has found narcissism, and especially its more maladaptive facets, to be associated with a rather broad set of internalizing problems, including symptoms of fear, worry, and depression (Barry & Malkin, 2010; Washburn, McMahon, King, Reinecke, & Silver, 2004). The exact pattern of links between narcissism and internalizing problems is rather complicated, however, with other facets of narcissism showing no or even negative associations with internalizing problems (Barry & Malkin, 2010).

Recent research sought to provide further clarification (Nelemans et al., 2015). A large community sample of schoolchildren (aged 8 to 14) completed measures of narcissism and self-esteem, as well as anxiety (i.e., symptoms

of social anxiety, generalized anxiety, separation anxiety, and panic) and depression. Using a latent class analysis it was possible to distinguish empirically between groups of children who were high in both narcissism and self-esteem (this group was labeled grandiose narcissism) and those who were high in narcissism but lower in self-esteem (this group was labeled vulnerable narcissism). Compared with other groups, children in the vulnerable narcissism group experienced elevated levels of overall anxiety and depression, whereas children in the grandiose narcissism group experienced lower levels of overall anxiety and depression. This pattern sustained longitudinally, such that vulnerable narcissism (but not grandiose narcissism) predicted increased overall anxiety and depression problems 1 year later. Thus, these results suggest that narcissistic children's level of self-esteem foretells how much they are at risk to suffer from anxiety and depression symptoms.

In summary, clinical writings and empirical research suggest that vulnerable manifestations of narcissism are, to a considerable extent, similar among youth and adults. Yet some manifestations may be especially salient in children and adolescents, including the predisposition to experience envy, shame, worthlessness, anxiety, and depression.

ASSESSMENT OF NARCISSISM IN CHILDREN AND ADOLESCENTS

Up until the early years of this century, empirical research on narcissism in children and adolescents was virtually nonexistent. The study of narcissism in youth was patented by clinicians who described the manifestations, consequences, progress, and treatment of narcissistic problems in their young patients. This status quo changed when the first standardized measures of trait narcissism became available that were specifically developed for children and adolescents (Barry et al., 2003; Frick, Bodin, & Barry, 2000). The availability of these measures has made it easier for researchers to study narcissism in youth. In this section, we discuss some common questions and concerns regarding the assessment of narcissism in youth, and review available measures.

Questions and Concerns

A number of questions and concerns are occasionally raised regarding the assessment of narcissism in youth, and we address them here.

1. *Do children who hold narcissistic traits actually report narcissistic traits?* One may perhaps suspect that scores on measures of youth narcissism will be strongly positively skewed, possibly because youth who hold narcissistic traits may not acknowledge or self-endorse their narcissistic traits; they might be concerned about the negative impression they would make on others by self-endorsing such traits (we anticipated this possibility when we started doing research on narcissism). Such suspicion seems unwarranted, however. Youth narcissism is a normally distributed trait, as has been found across different measures, across respondents of different ages (i.e., aged 8–18 years), and across samples of different types (e.g., community samples of typically developing youth and clinical samples of incarcerated youth; Barry & Wallace, 2010). Also, youth narcissism is unrelated to standard measures of social desirability, suggesting that social desirability or impression management concerns do not typically keep children and adolescents from reporting narcissistic traits (Thomaes, Stegge, et al., 2008).
2. *Is it ethical to assess narcissism in youth?* Two ethical concerns are sometimes raised regarding the assessment of youth narcissism in scientific research. First, it is argued that because aspects of narcissism may be relatively normative or age-appropriate in some stages of development, researchers assessing youth narcissism run the risk of problematizing patterns of thought, feeling, and behavior that are actually quite transient and innocuous. Second, it is argued that because the term narcissism has the connotation of being a stable, ingrained personality structure that is hard to overcome, researchers should use a different term.

   Although these concerns are understandable, we do not believe that simply refraining from assessing narcissism or using different terminology would be good solutions. First, it is true that aspects of narcissism are more age-appropriate in some stages of development than in others. For example, self-consciousness and egocentrism are aspects of narcissism that show normative developmental increases with the onset of adolescence. However, the same holds for other personality traits—in fact, it is the rule rather than the exception that there are stages in development when what appear as manifestations of maladjustment actually are age-appropriate phenomena. We believe that narcissism should be studied both in stages when it is more and less age-appropriate, as this may provide important insight into when levels of narcissism become atypical given an individual's age.

   Similarly, it is true that while relatively little is known on how stable narcissistic traits are in youth, the term

narcissism may inadvertently communicate that it is an ingrained, highly stable trait. Still, we do not believe that a change of terminology is recommendable. First, it would isolate research on youth narcissism from research on adult narcissism. Second, it would involve the risk of introducing confusion regarding the exact psychological phenomenon that the new label would cover, and how it would be similar to or different from the former label. Third, the change in terminology might not even bring about the intended change: New terminology to describe negative psychological phenomena may sound neutral when first introduced, but may easily gain the same connotations as its predecessor when it becomes more commonly used.

3. *Do we really need a measure of narcissism specifically developed for youth?* This question is occasionally asked, perhaps mainly by social-personality and clinical psychologists. The argument is that the field might be better off with a single measure of trait narcissism that would function as a gold standard. We agree that such a gold standard would facilitate the interpretation and generalization of findings across development, from childhood into adulthood. Also, if a gold standard were available, it would be easier to examine the developmental stability of narcissism, especially its mean level stability.

   Measures of youth narcissism are needed, however. First, and most prosaically, the wording of standard adult measures of narcissism is too complicated to be used with youth. For example, not all 8-year-olds will be able to understand such items as, "I like having authority over other people" (included in the NPI). Second, adult measures of narcissism often require relatively complex self-reflective skills—skills that are too complex for many children and adolescents. For example, not all children will be able to understand the statement that "It is hard for me to feel good about myself unless I know other people like me" (taken from the Pathological Narcissism Inventory). Third, as discussed in the *Manifestations* section, some key narcissistic characteristics manifest themselves differently in different stages of development: Developmental psychologists studying narcissism are hunting a moving target. For example, the items "People always seem to recognize my authority" (included in the NPI) and "I am a great example for other kids to follow" (included in the Childhood Narcissism Scale) likely tap a similar underlying narcissistic cognition (i.e., self-perceived authority), but the latter item is more age-appropriate and thus more meaningful for children. Thus, although a gold standard measure of narcissism would be ideal for pragmatic reasons, it is neither feasible nor desirable. The field benefits most from age-appropriate measures of narcissism.

4. *Does the assessment of youth narcissism add to the assessment of self-esteem?* At first blush, it may seem reasonable to assume that narcissism and self-esteem are strongly correlated, perhaps to such an extent that any variance they do not share is of trivial importance. Yet, although narcissists hold grandiose self-views and feel superior to others, they are not necessarily satisfied with the person they are. Indeed, correlations between youth narcissism and self-esteem are typically small, with *r*s often ranging between .0 and .30 (Barry & Ansel, 2011; Thomaes, Stegge, et al., 2008). Moreover, narcissism and self-esteem tend to have different correlates, supporting the notion that in many ways narcissism is the less adaptive cousin of high self-esteem (e.g., Barry et al., 2007; Thomaes et al., 2013). Also note that narcissism and self-esteem sometimes interact at predicting important outcomes, including the outcomes of aggressive behavior and symptoms of depression and anxiety, presumably reflecting the different consequences of grandiose (high narcissism and high self-esteem) versus more vulnerable (high narcissism and lower self-esteem) manifestations of narcissism (for a review, see Thomaes, Brummelman, Reijntjes, et al., 2013). Thus, the assessment of narcissism adds to the assessment of self-esteem.

Self-Report Measures of Narcissism for Children and Adolescents

Narcissism is a form of self-evaluation, so self-report is the method of choice to assess youth narcissism. It is only by means of self-report that key narcissistic characteristics, such as grandiose self-views, or the sense of entitlement and superiority, can be directly assessed.

Unsurprisingly, then, the standard measures of adult narcissism are self-report questionnaires. The NPI (Raskin & Hall, 1979; Raskin & Terry, 1988), in particular, has become the standard for the assessment of trait narcissism in adults in the social-personality and clinical literature. A more recent, promising measure of narcissism in adults is the Pathological Narcissism Inventory (PNI; Pincus et al., 2009). This measure was developed in response to the concern, voiced by some experts, that the NPI may assess relatively adaptive manifestations of narcissism. The PNI is developed with the goal of assessing more maladaptive manifestations, and it assesses both narcissistic grandiosity and narcissistic vulnerability.

To assess narcissism in youth using self-report there are two main measures: the Childhood Narcissism Scale (Thomaes, Stegge, et al., 2008) and the Narcissistic Personality Inventory for Children (NPIC; Barry et al., 2003). These measures are similar in that they aim to measure narcissistic traits in the general child and adolescent population (i.e., in children about age 8 and older), and that they have been well validated in multiple cultures. The main difference between the measures is their breadth of measurement and their length. No single measure of youth narcissism is preferable over the other—rather, both measures can be used for different purposes.

Childhood Narcissism Scale

The Childhood Narcissism Scale (Thomaes, Stegge, et al., 2008) is a short (i.e., 10-item) yet comprehensive measure of individual differences in trait narcissism. It can be used in community samples of children and adolescents aged 8 years and older. Sample items include, "I am a great example for other kids to follow," and "I love showing all the things I can do." Items are rated along a 4-point scale ranging from 0 (not at all true) to 3 (completely true).

A principal components analysis, parallel analysis, and confirmatory factor analysis conducted in representative community samples of Dutch children (aged 8–13) found that the CNS has a one-dimensional factor structure. The original Dutch version of the CNS has been translated and cross-validated in a community sample of children from the United States (aged 10–14 years). A confirmatory factor analysis found again that a one-dimensional structure underlies the CNS. Internal consistency of the CNS is good (with alphas typically ranging between .75 and .90), and 2- and 6-month test-retest reliability estimates of .76 and .69 have been found, respectively. Research on the psychological and interpersonal correlates of the CNS suggests that CNS-measured childhood narcissism fits in a largely similar nomological network as adult narcissism. The CNS is related to self-appraised superiority but virtually unrelated to self-esteem (i.e., individuals high in CNS-measured narcissism tend to feel superior to others, but are not particularly satisfied with themselves). Moreover, the CNS is associated with self-esteem contingency (i.e., the tendency to base one's worth as a person on approval from others), agentic but not communal social goals (i.e., the motivation to dominate social interactions and gain admiration, but not to establish close relationships), emotional extremity (the tendency to experience both positive and negative emotions frequently and intensely), other dark-triad personality traits (i.e., psychopathic and Machiavellianist personality traits), aggression, conduct problems, and reduced empathic concern (Barry & Wallace, 2010; Thomaes, Stegge, et al., 2008; Van Baardewijk et al., 2008).

Narcissistic Personality Inventory for Children

The NPIC (Barry et al., 2003) is a 40-item measure of individual differences in narcissistic traits. It is a downward extension of the NPI: Items closely mirror those from the original NPI, but some are adapted to make them more developmentally appropriate (for example, the original NPI item, "Modesty doesn't become me," has been changed to, "I like to show off the things that I do well"). The NPIC has been used in both community and clinical samples of older children and adolescents. Respondents first select one statement from a pair of statements (e.g., "I would rather be a leader" vs. "I don't care if I'm a leader or not"; and "I really like to be the center of attention" vs. "I'm not comfortable being the center of attention"), and then indicate whether the selected statement is sort of true or really true for them.

Whereas the CNS is primarily meant to assess narcissism as a single construct, the NPIC assesses narcissism as a multifaceted construct. Specifically, the NPIC can be used to distinguish between what has been labeled as adaptive and maladaptive narcissism. The Adaptive Narcissism subscale comprises 14 items that tap feelings of self-sufficiency and authority. The Maladaptive Narcissism subscale comprises 18 items that tap exhibitionism, exploitativeness, and entitlement (Barry, Frick, Adler, & Grafeman, 2007; Barry & Ansel, 2011). Although both subscales are relatively strongly correlated (with *r*'s typically ranging between .50 and .60), they have different correlates. Adaptive narcissism is associated with social skills, the quality of one's social relationships, and self-esteem; whereas maladaptive narcissism is associated with callous-unemotional traits, hyperactivity/impulsivity, conduct problems, delinquency, and reduced self-reliance (Barry & Ansel, 2011; Barry, et al., 2007; Barry & Wallace, 2010).

There has been some debate on what adaptive narcissism exactly means. Some have argued that the traits presumed to constitute adaptive narcissism, traits such as self-confidence, self-reliance, and self-perceived authority, often yield social rewards in present-day Western society and may be considered adaptive (Barry & Ansel, 2011). Others have argued that the traits that constitute adaptive narcissism represent nothing else than self-confidence—a trait that is associated with narcissism but is not inherent to it (Brown, Budzek, & Tamborski, 2009). These latter authors argued that it is important to distinguish

narcissism itself (which is essentially maladaptive) from the more adaptive, self-secure traits that are associated with it.

Additional Measures of Narcissism for Children and Adolescents

Antisocial Process Screening Device

The Antisocial Process Screening Device (APSD; Frick & Hare, 2001), a measure of psychopathic traits in youth, contains a 7-item Narcissism subscale. Some aspects of psychopathy, in particular the sense of grandiosity, are indicative of narcissism, and the APSD measures overt behaviors that reflect grandiosity. Sample items include, "Brags about accomplishments, abilities, or possessions," and "Thinks she/he is better or more important than other people." Items are rated along a 3-point scale ranging from 0 (not at all true) to 2 (definitely true). The APSD was originally developed as a parent- and teacher-report measure, but a self-report version was developed later (e.g., Vitacco, Rogers, & Neumann, 2003). APSD self-reported narcissism (sometimes labeled psychopathy-linked narcissism) is associated with both proactive and reactive aggression (even after controlling for the other psychopathy dimensions of callous-unemotional traits and impulsivity), delinquency and conduct problems, number of police contacts, but also with elevated levels of fear, worry, and depression (Barry & Malkin, 2010; Barry, Thompson, et al., 2007; Barry & Wallace, 2010; Munoz & Frick, 2007).

What is the utility of the APSD narcissism subscale for the assessment of narcissism in youth? The APSD has some practical benefits: It is short, and in some research settings it is advantageous that parent-, teacher-, and self-report equivalents are available. Moreover, the APSD is a preferred measure when researchers are specifically interested in assessing grandiosity features insofar as they relate to psychopathic traits. Yet if researchers are interested in narcissism per se, the APSD is not recommended. It assesses narcissistic behaviors, but not narcissistic cognitions and feelings (e.g., grandiose self-evaluations, feelings of entitlement) that are at the core of narcissism.

Observed Narcissism

Observational measures of narcissism are sometimes used, especially in analyses of existing longitudinal data sets that include observational measures of personality. For example, a set of 10 items from the California Adult Q-set (CAQ; Block, 1978), scored by a team of psychologists and advanced psychology students, has been taken to index narcissism in adolescent participants (Carlson & Gjerde, 2009). The items were selected based on their relatively strong correlations to the NPI as found in other research (Raskin & Terry, 1988), and includes such items as, "Genuinely submissive, accepts dominance comfortably" (reversed), and "Unaware of self-concern, feels satisfied with self." Observational measures can be useful to index narcissism in analyses of existing longitudinal data; they may allow researchers to explore the long-term stability or developmental precursors of narcissism (which is precisely what Carlson and Gjerde did). They may also be useful to measure early, rudimentary manifestations of narcissism or its precursors before they can be measured using self-report. Yet, observational measures are not ideal measures of narcissism in that, again, they only tap outward expressions of narcissism, not the internal narcissistic cognitions and feelings that are at the core of narcissism.

THEORIES OF NARCISSISM

Narcissists are individuals full of paradoxes. They feel superior to others but also crave others' admiration. They appear self-confident but are also easily threatened by criticism. They are charming but also insensitive to other people's needs. What personality constellation or psychological process may underlie these seemingly paradoxical traits? Over the years, several psychological theories of narcissism have been proposed in an attempt to answer this question. We will describe the most influential theories here.

Dynamic Self-Regulatory Processing Model

The dynamic self-regulatory processing model of narcissism (Morf & Rhodewalt, 2001) is the most influential model of narcissism to date. This model is based upon the assumption that people, narcissists and nonnarcissists alike, are universally invested with creating and maintaining desired self-views (sometimes called ideal selves). To that end, people employ a variety of inter- and intrapersonal self-regulatory strategies. According to the model, narcissists have the ultimate goal of building and maintaining a grandiose self. They want to feel superior, important, and influential, and they employ social, cognitive, and affective self-regulatory strategies to achieve this goal. Yet, narcissists achieve their goal only fleetingly, because their grandiose self-views are virtually impossible to maintain: In everyday life, narcissists, like anyone else, cannot avoid encountering information that falsifies their grandiose self-views, such as failure, criticism,

or rejection. Because narcissists' self-views are ultimately vulnerable, they need constant external validation, such as praise and admiration, to create, maintain, or rebuild their grandiose self. Thus, narcissists are in a chronic state of self-under-construction (Morf & Rhodewalt, 2001): They continuously employ a variety of inter- and intrapersonal strategies to create and maintain the grandiose self they so strongly desire.

On the *interpersonal level*, narcissists try to instil favorable impressions on others, and try to mold their social interactions such that they will receive others' attention and admiration. For example, they constantly try to be at the center of attention, to garner others' admiration, and to prove they are superior to others: Narcissists are more concerned with getting ahead than with getting along. On the *intrapersonal level,* narcissists seek to validate their grandiose self-views, such as by taking excessive credit for successes, by dismissing negative outcomes, by overestimating their competencies and accomplishments, and by reconstructing past experiences in self-flattering ways. Thus, narcissists are highly inventive in finding ways to build and buttress their grandiose self-views.

Ironically, however, narcissists' relentless attempts to gain external validation may ultimately prove self-defeating. Their attempts to garner attention, praise, and admiration may eventually backfire, and repel the very people on which they are dependent for approval. On first encounter, narcissists typically appear charming, confident, and easygoing. Eventually, however, the more adversarial narcissistic self may surface when narcissists manipulate others, act in arrogant ways, have trouble empathizing with others, and deal in selfish ways with conflicts of interest. Once others notice narcissists' adversarial interpersonal orientation, they may no longer serve as the source of external validation that narcissists need. This dynamic has been considered the ultimate *narcissistic paradox* (Morf & Rhodewalt, 2001): In seeking others' approval, narcissists tend to destroy the very relationships on which they are dependent. Much like Narcissus—who reached out for his own image in the water, touched it, and thereby made it disappear—narcissists' strategies to build grandiose self-views may be counterproductive and eventually undermine the grandiose self they are trying to create.

Discussion

The self-regulatory processing model has contributed to our understanding of narcissism in important ways. It was the first model to illuminate not only narcissists' stable traits and characteristics, but also the moment-to-moment self-regulatory strategies by which narcissists seek to achieve desired self-views. In doing so, the self-regulatory processing model bridges trait- and process-based approaches to personality (Morf & Rhodewalt, 2001). According to the model, narcissists' stable characteristics are rooted in the predictability of the momentary strategies they employ to build the grandiose self. A major contribution of the model is that it outlines how social, cognitive, and affective processes interact to create and maintain the grandiose self.

Importantly, key aspects of the model have been confirmed by research in children and adolescents. For example, recent research shows that narcissistic children easily lose self-esteem, that they desire admiration, and that they employ a variety of intra- and interpersonal regulatory strategies to create and maintain their desired self-views. The model is not without limitations, however. One caveat is that one of the model's key postulates—that narcissists have a vulnerable self—has received mixed theoretical and empirical support. Experts disagree about whether narcissists have a vulnerable self in the first place, and among those who do believe that narcissists might have a vulnerable self, there is disagreement about the nature of such vulnerability.

Taken together, the self-regulatory processing model is comprehensive, provides unique insight into the nature of narcissism, and has received considerable empirical support in child and adolescent samples. The nature of narcissistic vulnerability, however, needs further clarification.

Addiction Model

The addiction model of narcissism (Baumeister & Vohs, 2001) draws a direct parallel between narcissists' addiction to being admired and more familiar addictions (e.g., drug addictions). In this view, narcissism may not be a personality trait in the strict sense, but a chronic pattern of urges and behaviors that shares striking similarity to the urges and behaviors that characterize addiction. Addiction refers to a condition in which people need a stimulus (e.g., cocaine, alcohol, gambling) to avoid physical or psychological withdrawal symptoms (American Psychiatric Association, 1994). In seeking short-term gratification of their needs, addicted people risk long-term costs, such as to their interpersonal relationships. Similarly, in their seeking for admiration from others, narcissists may inadvertently destroy the very relationships on which they are dependent for obtaining admiration (Baumeister & Vohs, 2001). And much like addicts experience highs and lows, narcissistic individuals do not hold stable inflated self-views but

experience periods of self-view highs that feel very good, interspersed by periods of self-view lows that feel very bad (Thomaes et al., 2010; Thomaes, Stegge, et al., 2008).

More to the point, narcissism may share three hallmarks of addiction—cravings, withdrawal, and tolerance. *Cravings* refer to an intense longing for a desirable stimulus. Narcissists crave to be admired by others, and they use many different strategies to reach this goal, even strategies that harm other people. As such, narcissists' strategies to get their admiration fix are not unlike other addicts' strategies to get their fix. *Tolerance* refers to a decrease in the effects of a drug, so that increasing dosage is needed to yield similar effects. Similarly, narcissists never seem to be satisfied with a given level of admiration; even when they have received the admiration they strived for, they typically want even more admiration from more sources on more occasions. *Withdrawal* refers to the distress that ensues when administration of a drug is withheld. Similarly, when narcissists fail to elicit admiration from others, their self-esteem drops and they tend to become angry, hostile, or aggressive—not unlike addicts who are denied their fix.

Additional similarities between narcissism and addiction lie within the interpersonal domain. The state in which narcissists become shortsighted and preoccupied with garnering others' admiration has been labeled *narcissistic myopia* (Baumeister & Vohs, 2001). In such a state, narcissists may see others primarily as a means to obtain admiration, and they disregard others' needs and concerns. Also, when narcissists have received from the relationship what they desire, namely admiration, they often move on to another potential source of admiration (e.g., a new friend or partner). Narcissists may thus neglect depleted sources of admiration. Together, these adversarial interpersonal processes may cause narcissists to repel others and, consequently, to lose others' appreciation and admiration.

Discussion

The addiction model has originally been proposed as a conceptual addition to the self-regulatory processing model of narcissism (Morf & Rhodewalt, 2001). Unsurprisingly, then, it shares several strengths with this model—it sheds light on not only narcissists' traits, but also their moment-to-moment self-regulatory strategies. Despite this overlap, the addiction model has several unique features. First, it emphasizes that the core of narcissism is motivational: Narcissists do not primarily differ from nonnarcissists in *how they see themselves*, but in *what they strive for*. Second, the model might provide novel insight into the origins, nature, and consequences of narcissism. For example, it has been suggested that narcissism might have similar developmental pathways and neurobiological determinants as other forms of addiction (Thomaes, Brummelman, Reijntjes, et al., 2013). If so, then effective treatment of narcissistic maladjustment might benefit from building upon effective treatments of more typical forms of addiction. These and other predictions may inform prevention and intervention efforts to curtail narcissistic development.

The addiction model of narcissism has conceptual power and charm. Unfortunately, however, it has never been tested directly, neither in adults nor in youth. An important task for future research will be to test the model, and to determine whether the parallel between narcissism and addiction is more than just a useful metaphor.

Big-Five Model

Personality can be cast in terms of the five basic dimensions of Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism—collectively labeled the Big Five (e.g., Costa & McCrae, 1997). Paulhus (2001) has proposed a minimalist model of narcissism, which represents narcissism in terms of two Big Five personality dimensions: Agreeableness and Extraversion. Specifically, narcissists may be viewed as disagreeable extraverts. Disagreeable individuals tend to be interpersonally distrusting, egocentric, noncompliant, arrogant, and tough-minded. Extravert individuals are generally warm, gregarious, assertive, active, excitement seeking, and prone to experience positive emotion. Thus, disagreeableness and extraversion may jointly account for narcissists' antagonistic, noncommunal, agentic, energetic, and reward-focused traits.

Discussion

The strength of the Big Five model of narcissism lies in its parsimonious account of narcissism and its relying upon a long-standing line of theory and research on the structure of personality. The model does have its downsides, though. First, and importantly, it is unlikely to explain the full range of narcissistic traits. For example, it is unclear how joint disagreeable and extraverted traits may explain why narcissists hold unrealistically positive, inflated self-views. Similarly, joint disagreeable and extraverted traits do not explain narcissists' sensitivity to ego threatening experiences. Another downside is that the Big Five model does not further understanding of the intra- or interpersonal strategies that characterize narcissism. Direct evidence for the validity of Big Five model of narcissism in youth is still lacking. Future research should examine the extent to

which youth narcissism can be understood from the Big Five model, and what narcissistic traits can and cannot be explained from this model.

Psychoanalytic Models

In the early stages of theorizing about narcissism, psychoanalytic models were relatively influential. In particular, the object-relations model (proposed by O. F. Kernberg) and self-psychology model (proposed by Kohut) provided frameworks from which psychologists tried to understand narcissism. Both models are briefly described here.

Object-Relations Model

Object-relations theory assumes that people have two fundamental drives—libido and aggression. In addition, it assumes that people hold self-representations (i.e., internal images of themselves) as well as object-representations (i.e., internal images of important others). These representations contain good or positively valenced aspects (caused by libido) as well as bad or negatively valenced aspects (caused by aggression).

According to Kernberg (1975), narcissism comes in different forms depending on how people integrate positive and negative self- and object-representations. *Normal narcissism* arises, he thought, when people integrate both positive and negative aspects into their self- and object-representations. As such, normal narcissism is a normative process, and allows people to evaluate themselves and others realistically. By contrast, *pathological narcissism* arises when people integrate only positive aspects into their self- and object-representations, and project bad self- and object-representations onto others. Thus, pathological narcissism involves unrealistically positive, grandiose views of the self yet highly negative views of others. Because pathological narcissists devalue others, they cannot develop self-esteem that is based on approval from others, Kernberg argued; instead, narcissists need constant admiration to feel good about themselves.

Self-Psychology Model

According to the self-psychology model (Kohut, 1971), children are born in a state of self-love called primary narcissism. Primary narcissism was thought to be a manifestation of the fundamental human motive or instinct to survive. According to the model, children initially hold highly positive views of both themselves (i.e., the grandiose self) and their parents (i.e., the idealized parent image). Under optimal developmental conditions, the grandiose self gradually matures, and comes to form the root of people's ambitions and self-esteem. Similarly, the idealized parent image gradually becomes internalized into a superego—moral standards and values that influence the ideals that people come to hold. Yet, as Kohut argued, if children experience trauma (e.g., when their parents are insufficiently sensitive to their needs), the grandiose self and the idealized parent image may keep their infantile form, and ultimately give rise to pathological narcissism. Thus, the self-psychology model assumes that pathological narcissism arises from developmental arrest. Narcissists may relive their unfulfilled interpersonal needs and developmental tasks in their later interpersonal relationships. For example, in friendships or romantic relationships, they may constantly seek others' acceptance and recognition, in an attempt to affirm their grandiose self.

Discussion

Although the importance of psychoanalytic models of narcissism to contemporary empirical research has been relatively limited, some postulates of these models have been influential. First, psychoanalytic models emphasized that narcissists have distorted views of themselves and others. Empirical research suggests that distorted self- and other-views might be a central component of narcissism (Andersen, Miranda, & Edwards, 2001; Morf & Rhodewalt, 2001). Second, psychoanalytic models made the important distinction between narcissism and self-esteem, which is consistent with current conceptualizations and research findings. Third, psychoanalytic models were the first to illuminate the wide-ranging cognitive strategies that narcissists employ in the face of setbacks to maintain their positive self-views. Empirical research has confirmed that narcissists frequently employ such strategies as denial, rationalization, and externalization of blame (Morf & Rhodewalt, 2001). Fourth, psychoanalytic models adopted a developmental perspective on narcissism, while other theories more or less assumed, either implicitly or explicitly, that the nature of narcissism remains similar over the course of development. Psychoanalytic models attempted to understand narcissism from a life-course perspective, in which early disruptions in self-development might lead to narcissistic pathology in adulthood—an assumption that is influential up until today.

Conclusion and Future Directions

Given its paradoxical nature, narcissism poses an intriguing challenge to theorists: How to understand its seemingly incongruous constellation of traits from a single psychological perspective? From the early days of psychology, several

models have been proposed to explain the nature of narcissism, models that have yielded important and sometimes counter-intuitive insights. What is lacking from the most influential models of narcissism, however, is a developmental perspective. This is unfortunate for two main reasons. First, both the manifestations of narcissism and its underlying processes may change over the course of development. Second, a developmental perspective is needed to illuminate the mechanisms that link developmental antecedents (e.g., dysfunctional socialization experiences, temperamental diathesis) to later narcissism (Olson & Dweck, 2008). Knowledge of these mechanisms will facilitate prevention and interventions efforts to curtail narcissistic development at an early age.

DEVELOPMENT AND ETIOLOGY OF NARCISSISM

The earliest experiences of Narcissus, as recorded by Ovid, were timed when he "had just reached his sixteenth birthday, and could be thought of as either a boy or a man (Ovid, trans. 2010, p. 76)." *When* and *why* did Narcissus become the self-absorbed, self-loving person he was? Or, in more psychological terms, how did Narcissus' personality emerge and develop over time, and what environmental and constitutional factors contributed to its development? We do not know yet. Similarly, we know relatively little about the factors that lead children to develop narcissistic traits.

There has been relatively little research into the development and etiology of narcissism, yet theoretical models exist and empirical evidence is beginning to emerge. We will first describe the development of narcissism as a derailment of normal self-development. Then, we will discuss the two most influential theories of the socialization of narcissism—social learning theory and psychoanalytic theory. Then, we will discuss empirical evidence for these theories, and explain how research has been hampered by methodological challenges. Finally, we will propose an integrative, diathesis–stress framework in which narcissism can be understood as arising from temperament × environment interactions.

When Does Narcissism Emerge?

Developmental psychology has had a longstanding fascination with the self, a fascination that has yielded detailed knowledge on normal self-development. We propose that narcissism can be seen as a derailment of normal self-development (Thomaes, Brummelman, Reijntjes, et al., 2013; Thomaes, Bushman, Orobio de Castro, & Stegge, 2009), and so knowledge of normal self-development may provide important insights into the development of narcissism.

Narcissistic and Nonnarcissistic Selves

When trying to understand narcissism from a normal self-developmental perspective, the first question one needs to ask is how narcissists' selves exactly differ from nonnarcissists' selves. One critical difference is that narcissists have an unusually strong need for self-esteem. To be sure, the tendency to pursue and be concerned about self-esteem is universal (e.g., Sedikides, Gaertner, & Vevea, 2005). People generally desire to feel worthy and valuable, and to be viewed by others in favorable ways. In that sense, narcissists and nonnarcissists differ in the degree to which they pursue self-esteem. For example, whereas nonnarcissists' pursue self-esteem only in naturally occurring situations that leave room for it (e.g., when they can accomplish something worthwhile), narcissists continuously seek and create situations in which they can enhance their self-esteem (Morf & Rhodewalt, 2001). Similarly, whereas positive illusions and a tendency to avoid negative feedback are common among nonnarcissists, such self-regulatory strategies are potentiated among narcissists, who greatly overestimate their competencies and relative standing to others, and who routinely deny or discredit negative feedback or lash out aggressively when receiving negative feedback (Bushman & Baumeister, 1998; Morf & Rhodewalt, 2001; Thomaes, Bushman, et al., 2008).

Besides differences in degree, however, there may also be some qualitative differences in the ways narcissists pursue self-esteem. Whereas nonnarcissists are typically invested in establishing social connections, narcissists are typically invested in establishing social dominance to be able to feel good about themselves (Campbell, Rudich, & Sedikides, 2002; Thomaes, Stegge, et al., 2008). Narcissists are rarely interested in creating warm and intimate social bonds. Instead, they want to stand out from the crowd, and their attempts to establish superiority often come at the expense of others. Thus, we propose that narcissism can be seen as an extreme expression of the universal human need for self-esteem. This need is expressed both more intensely and sometimes qualitatively differently in narcissists when compared with nonnarcissists.

Normal Self-Development and its Implications for the Emergence of Narcissism

Obviously, the mere understanding of how narcissists' and nonnarcissists' selves may differ from one another does

not tell us *when* narcissism may first emerge in development. Normal self-development may provide insight into this question. From about age 2 or 3, children start to show rudimentary signs that they can evaluate attributes of themselves (Harter, 2006, 2012). These evaluations typically focus on observable and salient behaviors or abilities (e.g., "I can count"). Later in early and middle childhood, children learn to evaluate an increasing number of self-attributes. However, these evaluations remain qualitatively different from those of older children in that they tend to be unrealistically positive (young children are not well able to distinguish their ideal competencies from their actual competencies, or to compare their own competencies with those of others) and domain specific (young children are not well able to aggregate self-evaluations across different domains). Young children also have limited abilities to consciously and intentionally reflect on themselves. Thus, they cannot yet form self-esteem as defined by a conscious, global evaluation of one's worth as a person (Harter, 2006, 2012).

From around age 8, children have acquired cognitive capacities that have important ramifications for how they view themselves. First and foremost, from this age, developmental increases in self-reflection and abstract reasoning allow children to make global evaluations of themselves as a person and to form self-esteem (e.g., "I like myself as a person"; Harter, 2006, 2012). Individual differences in self-esteem now rapidly emerge, with a majority of children thinking positively about themselves and a minority thinking less positively about themselves (note that relatively few children start to think negatively about themselves in an absolute sense; Thomaes, Brummelman, Bushman, Reijntjes, & Orobio de Castro, 2014). Furthermore, in late childhood, children have acquired the capacities to evaluate themselves from the perspective of others (Harter, 2006, 2012), and to incorporate social comparison information into their self-evaluations (e.g., "I am quite good at soccer: better than most of my peers, but not as good as Daniel"). Perhaps as a result, children this age have generally outgrown the unrealistically positive self-views that are normative for younger children (Marsh, Craven, & Debus, 1998). Importantly, from age 8 up into adolescence, children also become increasingly motivated to create and maintain favorable self-views and to avoid unfavorable self-views. This emergent need for esteem, or self-esteem motivation, is manifest in a number of important ways. First, older children and adolescents become increasingly self-conscious and concerned about how they are viewed by others (Elkind, 1967; Harter, 2006, 2012). Second, they more easily experience such emotions as shame and humiliation, emotions that are intimately linked to the maintenance of self-esteem (Reimer, 1996). Third, they increasingly use impression management strategies (e.g., acting cool) to try to influence the opinions that others hold of them (Harter, 2006, 2012).

There are several things that the normal development of self-esteem and the motivations that surround it may tell us about the development of narcissism. First, if narcissism essentially is an extreme form of self-esteem motivation, then its first observable manifestations are unlikely to emerge before about age 8 (although the early developmental processes leading to narcissism may well operate before this age). Indeed, it is difficult to see how children could possibly be overly invested in pursuing self-esteem before they formed a conscious, global evaluation of themselves. Second, also from about age 8, children have learned to evaluate themselves from the perspective of others (Harter, 2006, 2012), a skill that likely underlies narcissists' cravings to be valued or admired by others. Third, at this same age, children have typically outgrown the unrealistically positive, inflated self-views that are normative for younger children, which makes the inflated self-views that are characteristic of narcissism nonnormative from this age.

To be sure, narcissism likely has its developmental origins in individual traits and experiences that are present from the earliest stages of life (as we will argue hereafter). However, based on what we know about normal self-development, we propose that narcissism (1) does not become manifest before about age 8, and (2) will often become manifest after a derailment of normal self-development.

Initial research findings support the notion that narcissism is manifest and measurable beginning at about age 8. Personality questionnaires administered to community and clinic samples of older children and adolescents have yielded robust and replicable clusters of traits characteristic of narcissism (Frick, Bodin, & Barry, 2000). Our own work has found good internal consistency and test–retest reliability estimates for self-reported narcissism in children aged 8 and older (Thomaes, Stegge et al., 2008). Moreover, narcissism has many similar manifestations in childhood and adolescence as it has in adulthood. Future research is needed to validate the claims that narcissism cannot be meaningfully identified before about age 8, and that narcissism often becomes manifest after a derailment of normal self-developmental processes.

Developmental Change in Narcissism

One other critical question is how narcissism changes over the course of development. Traditional views on

personality would hold that narcissism should be relatively stable over the life course, both in terms of the level or intensity of its manifestations (which refers to the concept of mean-level stability), and in terms of individual differences (which refers to the concept of rank-order stability). Accordingly, the *DSM-IV* defines disorders of personality, diagnosed in adulthood, as pervasive and inflexible (American Psychiatric Association, 2000). Most current views, however, cast personality as more dynamic, and recognize that environmental influences (e.g., parenting experiences, life events, societal changes) may have a substantial impact on changes in personality over time (e.g., Caspi & Shiner, 2006). Unfortunately, whether and how narcissism changes over time is one of the most understudied questions in this field of research. Important questions such as (1) how population levels of narcissism differ from one developmental period to the other; (2) whether narcissism is best viewed as a transitory or as a lifelong or recurrent phenomenon; and (3) whether early emerging narcissistic traits increase the likelihood that children will develop narcissistic pathology in adulthood are largely unanswered today. On a more positive note, now that adequate measures of youth narcissism have become available over the past decade, the study of long-term change in narcissism has become much easier than it was in the past. In the following, we review the empirical evidence that does exist on the mean-level and rank-order stability of narcissism. Note that this evidence exclusively concerns trait narcissism; evidence on the stability of pathological manifestations of narcissism or NPD, is virtually nonexistent.

Both psychological theory and lay conceptions suggest that narcissism is more common in some developmental stages than in others. In particular, adolescence is often believed to be a narcissistic developmental period. Indeed, most high school or university teachers can provide anecdotes on the self-absorbed or entitled behavior of some of their students. One teacher of English at an institution for higher learning in the United States found the following note, written by a student who was unhappy with the way his course was organized: "I showed up to class today but no one was there. Where was class?!?! You need to make announcement when you are changing the location of class!!! No one likes to have to dig your syllabus out every day or check their email for your last minute changes. I DID show up today and you have to count my paper as ON TIME. Please email me with an explanation" (retrieved from http://www.passiveaggressivenotes.com).

Consistent with lay conceptions and anecdotal evidence, psychological theorists have described adolescence as a period of narcissistic vulnerability (Bleiberg, 1994). Several normative developments that occur in adolescence (e.g., developmental increases in self-focus and concern over one's public image) may become manifest in traits and behaviors that, at least on the surface, seem narcissistic. Similarly, it has been argued that separation-individuation processes, by which adolescents navigate between seeking connectedness and separation from their parents, are similar to the narcissistic interpersonal dynamic of seeking independence and validation from others at the same time (Hill & Roberts, 2011). Finally, adolescents often construct so-called personal fables (Elkind, 1967): illusions of invulnerability (the belief that one cannot be harmed or injured), omnipotence (the belief that one has special authority or influence), or personal uniqueness (the belief that one has unique traits, and cannot be understood by other people), which share surface features with narcissistic illusionary beliefs.

The long-term longitudinal research that is needed to provide adequate answers on how narcissism changes over time—research that runs from middle childhood into old age—is lacking. Cross-sectional research involving adolescents and older participants does exist, however. The outcomes of this research are consistent with the view that levels of narcissism typically are high in adolescence and then decrease over time. A large study including adolescents and adults from around the world found a steep linear decrease in narcissism from adolescence into older age. The difference in narcissism between the youngest participants (i.e., midadolescents) and the oldest participants in the study (i.e., who were older than 50) was nearly a full standard deviation (Foster, Campbell, & Twenge, 2003). In another study (Roberts, Edmonds, & Grijalva, 2010), introductory psychology students were found to be considerably more narcissistic than their parents who, in turn, were more narcissistic than the students' grandparents. The mean difference in narcissism between students and their grandparents was even more than a standard deviation.

In addition, one longitudinal study (Carlson & Gjerde, 2009) zoomed in on the developmental stages of adolescence and emerging adulthood, and examined how mean levels of observed narcissism (a narcissism measure was derived from the California Adult Q-set; Block, 1978) changed between ages 14 and 23 years. This study found that observed narcissism increased significantly from middle adolescence into late adolescence, and then followed a downward trend from late adolescence into emerging adulthood. This suggests that trait manifestations of narcissism may reach a normative peak in late adolescence and decrease from then on.

The putative trend for narcissism to be relatively high in adolescence and decline later has been interpreted in terms of the social investment model of personality trait development (Hill & Roberts, 2011). According to this model, changes in personality traits over time can be understood as normative developmental adaptations that allow individuals to take up age-appropriate roles. In adolescence, individuals need to develop an autonomous identity and set important personal goals with long-term relevance (such as deciding on a career to pursue; Collins & Steinberg, 2006). These developmental tasks might be facilitated when individuals adopt a rather narrow self-focus, characteristic of narcissism. From early adulthood onward, however, individuals typically commit themselves to such roles as being a husband, a father, and a colleague: roles that require them to take up a more communal, collectively responsible orientation, and to become less self-focused and narcissistic. Accordingly, from the perspective of the social investment model, narcissism is relatively high in adolescence because a self-focused, independent orientation might help individuals to form an autonomous identity. Narcissism then becomes considerably lower in adulthood because an other-focused, interdependent orientation might help individuals to take responsibility for their family, work, or community.

Importantly, the developmental trend of narcissism is different from that of self-esteem. Self-esteem typically is relatively high during childhood, drops sharply during adolescence, and then gradually increases throughout adulthood (Robins & Trzesniewski, 2005). Thus, adolescence might be a time when narcissism reaches its developmental high and self-esteem reaches its developmental low. Note that the combination of high narcissism and lower self-esteem reflects vulnerable narcissism, and so it may be no surprise that a number of hallmark features of vulnerable narcissism, including self-consciousness, social hypervigilance, and proneness to experiencing negative self-feelings, are more common during adolescence than during other developmental phases. Future research will need to examine whether it is specifically vulnerable narcissism—more than grandiose narcissism—that is high in adolescence.

A related, important set of questions concerns the rank-order stability, or stability of individual differences in narcissism (or its rudimentary manifestations) over the life course. Is it possible to identify early emerging individual differences in temperament that are linked to later narcissistic development? And when individuals are relatively high in narcissistic traits at one point in childhood or adolescence, then how likely are they to develop more ingrained narcissistic personalities later in life? Initial empirical evidence is beginning to emerge, and we will review that evidence here.

Personality theory and research has suggested that the earliest antecedents of personality traits and disorders can often be traced back to early childhood (American Psychiatric Association, 2000; Caspi & Shiner, 2006). Of course, this does not mean that personality already takes its mature, crystallized form in early childhood. It does imply, however, that it may be viable to try to identify broad temperamental traits at this age, traits that may lay the groundwork from which later personality structures, such as narcissism, emanate.

Following this reasoning, one longitudinal study used data from the Block and Block longitudinal project (Block & Block, 1980) to try to predict narcissistic traits in adolescence and emergent adulthood (ages 14, 18, and 23) from preschool personality attributes (Carlson & Gjerde, 2009). One strength of this study lies in the rigorous way personality was observed. At the preschool age, participants (N = 103, ages 3 and 4, recruited from nursery schools) were described by trained nursery school teachers using the California Child Q-set (CCQ, Block & Block, 1980), a Q-sort procedure consisting of a variety of statements about children's personality, cognitive, and social characteristics. Based on a priori expectations, five scales were derived from the CCQ that were anticipated to predict narcissistic traits in adolescence and emergent adulthood: (1) Interpersonal Antagonism (e.g., is aggressive; is considerate and thoughtful of other children [reversed]); (2) Center of Attention (e.g., tries to be the center of attention; is shy and reserved, makes social contacts slowly [reversed]); (3) Activity (e.g., is physically active; is vital, energetic, and lively); (4) Histrionic Tendencies (e.g., is emotionally labile; tends to exaggerate mishaps); and (5) Undercontrol of Impulse (e.g., is unable to delay gratification, cannot wait for satisfactions; overreacts to minor frustrations, is easily irritated and/or angered).

Years later, when participants were 14, 18, and 23, they were again described using a similar, age-appropriate Q-sort procedure, the California Adult Q-set (CAQ; Block, 1978), this time by advanced psychology students who did not know the participants before, but who intensively interviewed and observed them. From the Q-sort procedure, a narcissism measure was derived containing items known to correlate highly with the NPI (e.g., unaware of self-concern, feels satisfied with self; behaves in an assertive manner; and expresses hostile feelings directly). Importantly, the five preschool personality predictors were

significantly correlated with observed narcissism 10 to 20 years later.

A later study provided a conceptual replication (Cramer, 2011), and relied on the same dataset and preschool personality antecedents to predict narcissism at age 23 as indexed by a different set of CAQ items. In particular, this study distinguished between CAQ items reflecting what the authors labeled maladaptive narcissism (e.g., pushes and tries to stretch limits and rules; is self-indulgent; tends to "spoil" or pamper him or herself) and healthy narcissism (e.g., values own independence and autonomy; sets high personal goals; and is ambitious). It was found that the preschool attributes (i.e., antagonism, center of attention, activity, histrionic tendencies, and under control of impulse) specifically predicted maladaptive narcissism, but not its more adaptive counterpart.

Extending studies on the stability of observed narcissism, another study has provided insight into the stability of reported narcissism, in this case narcissism as a dimension of trait psychopathy (Frick, Kimonis, Dandreaux, & Farell, 2003). Narcissism is one dimension of psychopathy (callous-unemotional traits and impulsivity are the other psychopathy dimensions), and standard measures of youth psychopathy have a narcissism subscale. The Antisocial Personality Screening Device (Frick & Hare, 2001), a self-, parent-, and teacher-report measure that contains such items as "Thinks he/she is more important than others" and "Brags about abilities" was used in this study.

Participants were children and young adolescents (third to seventh grade) at the start of the study. Their parents rated their narcissistic traits annually for four years. Stability estimates for narcissism were quite high, with an intra-class correlation coefficient of .92 across all time points. Thus, a substantial amount of variance in parent-reported narcissism was consistent over time. Participants themselves also rated their narcissism at later time points. Although cross-informant (i.e., from parent-report to self-report) stability was considerably lower than within-informant stability, it still indicated that a substantial amount of variance in narcissism was consistent over time, with an intraclass correlation coefficient of .65 across time points. As the authors note, these stability estimates are somewhat higher than those typically found for child and adolescent personality measures.

Together, these results provide tentative empirical evidence to suggest that individual differences in narcissism may be quite stable over time—with preschool temperamental traits predicting individual differences in narcissism up into young adulthood, and parent- and self-reported narcissism being at least as stable as other forms of personality in late childhood and adolescence. Still, the research that has been done to date has limitations. First, the measures of narcissism that were used are unlikely to tap the full range of narcissistic characteristics. Both the Carlson and Gjerde study and the Cramer study relied on observational measures of narcissism. Observational measures are adequate to tap outward and observable narcissistic characteristics (manifest in behaviors or emotional expressions), but not internal narcissistic characteristics (thoughts and feelings). Similarly, the Frick et al. study focused on psychopathy-linked narcissism. Psychopathy-linked narcissism is distinct from normal subclinical narcissism in that it does not entail internal and vulnerable narcissistic manifestations. Thus, replication using standard, more comprehensive measures of narcissism is needed. Second, what is missing is longitudinal research that continuously follows up on narcissistic development from early age up into adulthood. Such research would allow researchers to answer to what extent youth who develop narcissistic traits are likely to remain narcissistic in adulthood, or even meet the criteria for NPD diagnosis. As the evidence stands, we cannot answer this important question conclusively.

Why Does Narcissism Emerge?

We have addressed the question of *when* narcissism may emerge, and now turn to *why* narcissism may emerge. The two most influential theories of the etiology of narcissism—social learning theory and psychoanalytic theory—emphasize that dysfunctional socialization experiences during childhood impact the emergence and development of narcissism.

Social Learning Theory

According to social learning theory (Millon, 1969), children acquire their self-views by observing and internalizing the way they are seen and treated by their parents. Specifically, social learning theory holds that parents cultivate narcissism in their children by overvaluing them—thinking that their children are more special and more entitled than other children are, and treating them accordingly. Our recent research shows that parents who overvalue consider their child to be superior to others, overclaim their child's knowledge, perceive their child as more gifted than actual IQ scores justify, want their child to stand out from others, and frequently praise their child in real-life settings (Brummelman, Thomaes, Nelemans, Orobio de Castro, & Bushman, 2014). Millon (1969) noted that parents of a future narcissist often see and treat their child as "God's

gift to man" (p. 263). Such socialization experiences might eventually lead children to internalize inflated, narcissistic views of themselves as extraordinary beings entitled to special treatment, admiration, and subservience from others (i.e., my wish is your command).

Millon (1969) also proposed that children who develop narcissistic traits often occupy a central position within the family, most notably the position of an only child (or, in certain cultures, the first male child). In line with the notion of the only child being spoiled, Millon believed that children with an only child status are often of special value to their parents and often are not subjected to the same restrictions and responsibilities as most other children. Consequently, Millon thought, only children may be more likely than other children to develop narcissistic traits.

Psychoanalytic Theory

Psychoanalytic theory holds that narcissists' inflated self-views are compensations for early deprivations in the parent-child bond. According to this perspective, narcissism develops in response to parents lacking warmth (e.g., being cold and unresponsive). Psychoanalytic theorists believe that narcissistic children have turned to themselves to obtain the warmth and approval they failed to receive from their parents. The theorists disagree, however, about the exact mechanisms through which such cold upbringing leads to narcissism. The disagreement between Kohut and Kernberg is of particular importance. Kohut (1971) argued that it is normative for infants to have an overly positive, grandiose self. This grandiose self needs to be mirrored by parents: Parents need to be sensitive and responsive to the child's unique experiences. When they do, children gradually develop more mature, realistic self-views. When they do not, children's self-views remain inflated, which might eventuate in later narcissism. In this view, narcissism represents an arrest of normal self-development.

From a different perspective, Kernberg (1975) argued that people hold both object-representations (i.e., internal images of important others) and self-representations (i.e., internal images of themselves). In healthy development, he argued, children internalize both positive and negative object and self-representations. In narcissistic development, children may internalize only positive object and self-representations, a process from which narcissism might emerge. At the same time, Kernberg argued, narcissistic children devalue negative object and self-representations (e.g., by projecting them onto others, leading to negative views of others). Because narcissistic children lack healthy object representations, they experience an internal void, a feeling of emptiness—which, so Kernberg held, they can compensate for by garnering praise and admiration from others. Moreover, much like Millon, Kernberg believed that future narcissists often occupy a central role within their family (e.g., they are only children, or considered by their parents to be particularly talented, special, or good-looking).

Taken together, Kohut proposed that narcissism represents arrested self-development, whereas Kernberg proposed that narcissism represents pathological self-development. They agreed, however, that narcissists' inflated self-views and strong need for external validation stem from dysfunctional socialization experiences.

Empirical Evidence

Both perspectives—social learning theory and psychoanalytic theory—have received preliminary empirical support, though mainly from research in adults. Retrospective, cross sectional, and prospective research suggests that narcissism is associated with parental overvaluation and the parenting practices that follow from it, such as permissiveness and indulgence. For example, retrospective studies show that adult narcissists have childhood recollections of their parents overvaluing them—putting them on a pedestal, having overly positive views of them, excessively praising them, and rarely criticizing them (Otway & Vignoles, 2006; but see Horton & Tritch, 2014). Adult narcissists also remember their parents being permissive (Ramsey, Watson, Biderman, & Reeves, 1996), overly indulgent (Capron, 2004), and rarely keeping track of their activities (Miller & Campbell, 2008). In addition, cross sectional research shows that older adolescents and young adults often perceive their parents as providing praise and tangible rewards (Mechanic & Barry, 2015), as warm, and (although less conclusively) as rarely monitoring them (Horton, Bleau, & Drwecki, 2006). Cross sectional research among 9-to-15-year-olds shows that narcissism is associated with both self- and parent-reported parental permissiveness (Barry et al., 2007). Finally, prospective research shows that some narcissistic traits (e.g., observer-rated traits of high aspirations and desire for autonomy) at age 23 are related to parent-reported permissive and indulgent parenting at age 3 (Cramer, 2011), suggesting that perhaps narcissism is rooted in early socialization experiences. Together, these studies provide preliminary evidence consistent with the social-learning perspective that holds that narcissism is cultivated by parental overvaluation and related parenting practices.

There is also preliminary evidence for predictions made by psychoanalytic theory. Retrospective and cross sectional research suggests that narcissism is associated with

parental lack of warmth, including coldness and unresponsiveness. For example, retrospective research indicates that adult narcissists have childhood recollections of their parents being cold, indifferent, and spiteful towards them (Otway & Vignoles, 2006). Other retrospective research indicates that adult narcissists, specifically those high in entitlement or grandiosity, have childhood recollections of their parents exerting harsh discipline, threatening with separation, and failing to provide a secure base (Cater, Zeigler-Hill, & Vonk, 2011). In addition, cross sectional research shows that adults with narcissistic traits, especially those with vulnerable narcissistic traits, perceive their parents as psychologically controlling (e.g., withdrawing their love when their children do not conform to their expectations; Horton et al., 2006; Miller & Campbell, 2008). Together, there is some evidence consistent with the notion that narcissism is influenced by parental lack of warmth and related parenting practices.

Thus, the available research suggests that multiple socialization experiences may be involved in cultivating narcissism. It has been suggested that "narcissistic traits can develop, curiously, when there are deviations from ideal rearing on either side: pampering or neglecting; expecting too much or too little" (Stone, 1993, p. 260). Either way, parents are ultimately insensitive and unresponsive to their child's needs and behaviors (Morf & Rhodewalt, 2001). These findings are in line with the concept of *equifinality*: Multiple developmental pathways (rather than a single pathway) may lead to a similar constellation of traits or disorder (Cicchetti & Rogosch, 1996). An important task for future prospective longitudinal research, from both a basic research and applied perspective, is to identify the multiple pathways that lead to narcissism. An improved understanding of the origins of narcissism will help explain the purpose of narcissists' self-regulation, which may partially arise from needs that were thwarted during childhood (Morf & Rhodewalt, 2001). In addition, an improved understanding of the origins of narcissism is needed to help practitioners devise developmentally tailored interventions to prevent or curtail narcissistic traits at a young age.

Millon and O. F. Kernberg proposed that narcissists often are only children. There is mixed support for this notion. Preliminary studies did not find evidence for birth order effects on narcissism (Curtis & Cowell, 1993; Eyring & Sobelman, 1996; Joubert, 1989; Narayan, 1990). Yet, these studies lacked sufficient sample size to detect birth order effects on personality, effects that are typically very small (for methodological considerations in birth order research, see Paulhus, 2008). Researchers have recently overcome this limitation by conducting two studies in large Chinese samples (N= 10,655 and 15,522; Cai, Kwam, & Sedikides, 2011). Both studies demonstrated a small yet robust link between only child status and narcissism (Cohen's d = .12 and .14, respectively, $p < .001$). These findings may not necessarily generalize to other cultures, however. Many Chinese families are subject to the one-child-per-family policy, implemented by the Chinese government in 1978 to control population size. It is possible that only-child status has different social and psychological consequences for children growing up in China than for children growing up in other countries.

Future research needs to further uncover the mechanisms that explain the potential link between birth order and narcissism, and a few questions seem of particular importance. Does only-child status actually foster narcissism in children, or are parents who are genetically more likely to have narcissistic children somehow more likely to have only one child? And if only-child status indeed fosters narcissism, is such influence mediated by parenting practices, such as increased overvaluation, indulgence, or permissiveness towards children with an only-child status?

Limitations of Previous Research

Previous research on the socialization of narcissism has been informative, and provided glimpses into the origins of narcissism. Yet it also suffered from methodological limitations. First, with some exceptions (e.g., Barry et al., 2007), previous research has mainly relied upon self-reports of experienced parenting. This might be problematic when studying narcissism, to the extent that narcissists' self-enhancing tendencies generalize to how they perceive or report on their parents' behavior towards them. Other-reported and observational measures are needed to index narcissists' socialization experiences. Second, previous research has mainly been cross sectional. Findings have been typically interpreted as showing that parenting practices affect children's narcissism, but the reverse pattern (i.e., children's narcissism affecting parenting practices) may of course be plausible as well. In fact, is it quite likely that narcissistic children's attempts to mold their social interactions (e.g., squeezing out admiration from others) affects the way their parents raise them. Longitudinal research is needed to study the transactions between children's narcissism and their socialization experiences, and to better understand temporal ordering. Third, previous research has been conducted mostly among college students, while the early developmental origins of narcissism probably lie in childhood. To uncover the origins of narcissism, research must investigate its development and socialization in childhood.

Temperament–Environment Interactions

One other limitation of previous research is that it did not take into account that some children, due to constitutional factors, might be more susceptible to socialization experiences than other children. Twin studies found that trait narcissism, measured in adults, is moderately heritable (Luo, Cai, Sedikides, & Song, 2014; Vernon, Villani, Vickers, & Harris, 2008), and that NPD is more heritable than any other personality disorder (Livesley, Jang, Jackson, & Vernon, 1993). Similarly, researchers have argued that the development of narcissism will at least be partially rooted in temperamental traits (Elliot & Thrash, 2001).

Temperament refers to early emerging, constitutionally based individual differences in how children react to their environment and how they control or regulate these reactions (Rothbart & Bates, 2006). From the earliest stages of development, temperament shapes and is shaped by children's experiences, thereby laying the foundation for personality (e.g., Rothbart & Bates, 2006). Crucial for understanding individual differences in narcissism are temperamental dimensions involved in the motivation of emotion and behavior. Research in children as well as adults has identified two fundamental motivational systems: *approach motivation*, which facilitates behavior toward desirable outcomes; and *avoidance motivation*, which facilitates behavior away from undesirable outcomes (Elliot & Thrash, 2002; note that different labels have been used for these motivational systems; see Rothbart, Ahadi, & Evans, 2000).

Approach Temperament

Approach temperament refers to a sensitivity to rewarding (e.g., positive, desirable) stimuli, accompanied by vigilance for, emotional reactivity to, and behavioral inclination toward such stimuli (Elliot & Thrash, 2002). Individuals high in approach temperament are sensitive to desirable stimuli, feel attracted to them, and react strongly to their presence or absence. Approach temperament appears to be based on brain systems previously labeled Behavioral Approach System, SEEKING system, or extraversion/surgency (for an overview, see Rothbart et al., 2000). Approach temperament can be observed from early development onward. Between 3 and 13 months of age, it is manifested by children smiling, laughing, vocalizing, and displaying motor activity (Rothbart, 1989), and it predicts actual behavioral approach (e.g., quickly reaching out for desirable objects, such as toys; Rothbart, 1988). Later in development, children high in approach temperament tend to approach desirable stimuli rapidly, are physically active, quickly feel at ease in new social settings, and prefer situations that involve intense stimuli (Rothbart et al., 2000). During adolescence, approach temperament can become evident in risk behavior, such as drug or alcohol use and risky sexual behavior (e.g., Zuckerman & Kuhlman, 2000). Although the manifestations of approach temperament change throughout development, individual differences in these manifestations are relatively stable over time (Rothbart & Bates, 2006).

Avoidance Temperament

Avoidance temperament refers to a sensitivity to punishing (e.g., negative, undesirable) stimuli, accompanied by vigilance for, emotional reactivity to, and behavioral inclination away from such stimuli (Elliot & Thrash, 2002). Individuals high in avoidance temperament are sensitive to undesirable stimuli, feel dispelled from them, and react strongly their presence or absence. Avoidance temperament appears to be based on brain systems previously labeled Behavioral Inhibition System or FEAR system (Rothbart et al., 2000). In the earliest months of life, infants high in avoidance temperament are prone to express fear and frustration and tend to inhibit their responses to novel and high-intensity stimuli (Rothbart, 1986, 1988). Later in development, avoidance temperament predisposes children to experience negative emotion (Rothbart et al., 2000). Although the manifestations of avoidance temperament change throughout development, individual differences in avoidance temperament are relatively stable (Rothbart & Bates, 2006). For example, children who are classified as inhibited at age 3 are more socially anxious during adolescence (Schwartz, Snidman, & Kagan, 1999) and more cautious at age 18 (Caspi & Silva, 1995).

Temperament and Narcissism

There are theoretical and empirical reasons to presume that narcissistic children are high in approach temperament. First, narcissists display many characteristics that are known to be associated with high approach temperament, including aggression (Bushman & Baumeister, 1998; Thomaes, Bushman, et al., 2008), impulsiveness, risk taking, extraversion (Paulhus, 2001), and dominance (Paulhus & Williams, 2002). Second, the early childhood precursors of narcissism are typical of high approach temperament. Prospective observational research indicates that children who later become narcissistic tend to be impulsive, physically active, and attention seeking during preschool years (Carlson & Gjerde, 2009). Third, much like individuals high in approach temperament, narcissists are highly sensitive to reward. Adult narcissists are at increased risk for gambling problems, are prone to making risky stock market investments, and are at increased risk to

using drugs (e.g., Stinson et al., 2008). Fourth, theories of narcissism emphasize that narcissists' pursuit of praise and admiration resembles a pattern of addiction (Baumeister & Vohs, 2001). Intriguingly, and in line with this idea, recent research found that people high in entitlement (a core dimension of narcissism) especially strongly desire to be praised by others (Bushman et al., 2011).

The link between narcissism and avoidance temperament is less straightforward. If anything, narcissists tend to show marked individual differences in avoidance temperament. For example, narcissistic children differ markedly in their tendency to experience negative affect, to dwell upon criticism and rejection, and to suffer from episodes of self-derogation (e.g., Thomaes et al., 2010, 2011; Nelemans et al., 2015). We propose that narcissists' differences in avoidance temperament may account for grandiose and vulnerable manifestations of narcissism (Foster & Trimm, 2008; Thomaes, Bushman, Orobio de Castro, & Stegge, 2009). Although this has not been investigated in children or adolescents, it is theoretically plausible that grandiose narcissism is rooted in high approach temperament and low avoidance temperament. In contrast, vulnerable narcissism may be rooted in both high approach temperament and high avoidance temperament. Thus, the level of avoidance temperament may be a key distinction between the two faces of narcissism (Foster & Trimm, 2008).

Integrative Model

Children vary in how much they are affected by environmental influences. Dual-risk models (Sameroff, 1983) and diathesis–stress models (Monroe & Simons, 1991) propose that some children, due to their vulnerable or susceptible personality makeup, are more strongly affected by environmental stressors than other children, thereby making them more prone to derailments of healthy social and emotional development. There is now ample evidence that temperament may determine children's susceptibility to socialization influences (for an overview, see Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2011).

We propose a diathesis–stress model of the development of narcissism, which casts narcissism as an addiction to admiration from others. The model holds that dysfunctional socialization experiences (i.e., socialization stress) may activate a latent, biologically based vulnerability to become overly dependent on rewarding stimuli, including rewarding social stimuli such as praise and admiration (i.e., the diathesis; Thomaes, Brummelman, Reijntjes, et al., 2013; Thomaes, Bushman, Orobio de Castro, & Stegge, 2009). From early development onward, individuals high in approach temperament are biologically wired to be sensitive to rewarding stimuli. When these individuals experience little socialization stress, their diathesis may remain dormant. However, when they experience much socialization stress, they may develop addictive problems (e.g., Goeders, 2003). In the particular context of an upbringing characterized by overvaluation or coldness, children high in approach temperament may become overly dependent upon receiving validation from others to feel good about themselves, a dependency that is central to narcissism. That is, narcissism may originate from joint dysfunctional socialization experiences and high approach temperament—an amalgam that may make children overly dependent on (or addicted to) praise and admiration from others.

The parallel between narcissism and addiction may reach even further, and account for the processes involved in the maintenance of narcissism over time. Repeated drug use causes persistent changes in the brain underlying sensitization (i.e., the process that makes individuals hypersensitive to the motivational effects of the drug; Robinson & Berridge, 2008). This neural sensitization causes addicts to become relapse-prone whenever they encounter drug-related cues, even if they have been clean for years. Analogously, it is possible that narcissists become sensitized to admiration, and therefore have difficulty resisting its allure, even after a period of abstinence (e.g., when they have obtained little admiration from their classmates for weeks). Another process that maintains drug use is withdrawal: Quitting drugs causes addicts to experience withdrawal symptoms, including restlessness, anxiety, and depression. Taking drugs alleviates these painful feelings (Koob & Le Moal, 2005). Narcissists may likewise strive for admiration to alleviate lurking feelings of anxiety and depression that may arise when they fail to feel admired. Taken together, we putatively suggest that the addiction-related processes of sensitization and withdrawal may at least partially underlie the maintenance of narcissism.

We hope this chapter will encourage researchers to contribute to the study of the etiology and development of narcissism. Knowledge of when and why narcissism emerges is not only of basic interest; it will also pave the way for prevention and intervention efforts to reduce narcissistic maladjustment.

CLINICAL PERSPECTIVES ON NARCISSISM

Throughout this chapter, we have drawn on both social-personality and developmental research on trait narcissism, and on clinical observations and research on

narcissistic pathology. The study of trait and pathological narcissism has remained relatively separated thus far (Cain et al., 2008). This is unfortunate. An integrative, interdisciplinary approach is needed to increase our understanding of what exactly distinguishes normal and pathological narcissistic functioning at different stages of development. Moreover, an interdisciplinary approach would facilitate our understanding of the psychological and developmental processes by which normal self-development can go awry and lead to narcissistic pathology.

Thus, given the current state of the literature, it would be premature to try to provide a comprehensive account of pathological narcissistic development, its origins, and outcomes. Rather, in the following section, we will address a number of issues that are important to understanding narcissistic pathology and its treatment. First, we will address the issues of whether or not NPD can or should be diagnosed in youth, and how NPD is different from related forms of personality characteristics and disorders. Next, we will review clinical and basic research approaches to intervening with narcissism and its consequences.

Pros and Cons of Diagnosing Narcissistic Personality Disorder in Children and Adolescents

The *DSM-IV* (American Psychiatric Association, 2000) discourages clinicians from diagnosing NPD (as well as other personality disorders) in children and adolescents. At the same time, it leaves open the possibility of NPD diagnosis in youth by noting:

> Personality Disorder categories may be applied to children or adolescents in those relatively unusual instances in which the individual's particular maladaptive personality traits appear to be pervasive, persistent, and unlikely to be limited to a particular developmental stage or an episode of an Axis I disorder. . . . To diagnose a Personality Disorder in an individual under age 18 years, the features must have been present for at least 1 year. (P. 687)

Thus, although the *DSM* warns against diagnosis of NPD before adulthood, it ultimately leaves the decision on whether or not to apply such a diagnosis in individual cases up to the clinicians' professional expertise. Perhaps as a result of that ambiguity, clinicians use the NPD diagnosis relatively rarely to classify the problems of their young patients, with psychiatric population prevalence estimates ranging from 0 to 3% in samples of adolescents (Tromp, 2010; Westen, Shedler, Durrett, Glass, & Martens, 2003). Yet, in studies that have used structured interviews or other standardized assessment procedures to measure specific symptoms of personality pathology, greater proportions of youth appear to meet the criteria for NPD diagnosis, with both psychiatric and general population prevalence estimates ranging from 6 to 9% in samples of adolescents (with the highest prevalence estimates found in boys in their early adolescence; Bernstein et al., 1993; Eppright, Kashani, Robison, & Reid, 1993). These figures suggest that narcissistic pathology may be relatively prevalent among youth, yet clinicians only rarely diagnose it as such (Westen et al., 2003).

To be sure, most clinicians and researchers agree that NPD typically has its onset in late childhood or adolescence. Patients do not start to suffer from narcissistic pathology at their eighteenth birthday—they often grow up as individuals who deviate, to some extent, from the expectations of their culture, and experience impairment in important domains of functioning. Yet, there is disagreement on whether it is sensible, even in extreme cases, to actually assess and diagnose NPD in children and adolescents.

One important reason to diagnose children or adolescents with NPD, is that such a diagnosis may, in certain cases, facilitate adequate support and treatment. Accurate diagnosis might help youth to get appropriate, specific treatment for their NPD symptoms and the conditions sustaining those symptoms. Such treatment might help prevent individuals from developing more crystallized and hard-to-treat forms of narcissistic pathology later in life. Also, more prosaically, insurance companies may be more likely to cover treatment of narcissistic pathology among youth when formally diagnosed. Finally, diagnosis may sometimes help patients and their close others to be more acknowledging or accepting of their problems and be more committed to treatment. They may be less likely to trivialize the traits that cause their impairment as unimportant when these traits have a name. Thus, when patients have difficulty acknowledging their problems, which is not unusual among narcissistic individuals, this may be reason for clinicians to actually apply the NPD diagnosis.

Yet of course there is also good reason to be cautious with diagnosing children and adolescents with NPD. First, a personality disorder diagnosis connotes pervasive and long-term psychological maladjustment that is difficult to treat, while clinicians of young patients are typically unsure of how symptoms will develop over time, and how well their patients will respond to treatment. Similarly, thorough empirical knowledge of the stability of narcissistic pathology from childhood or adolescence into adulthood is lacking (though preliminary evidence has suggested that dimensionally measured narcissistic pathology may

show considerable stability from early adolescence into early adulthood; Crawford, Cohen, & Brook, 2001). Thus, clinicians should be wary of premature NPD diagnosis. Second, even in individual cases when NPD diagnosis is not premature, it entails a risk of stigmatization. Youth diagnosed with NPD may come to feel aberrant, weird, and chronically debilitated, or they may come to be seen in such a light by others. As detailed elsewhere (Hinshaw, this Volume), stigmatization can lead to feelings of shame or self-blame and social distance—factors that might exacerbate rather than alleviate patients' symptoms. In fact, because the very nature of narcissism involves a heightened sensitivity to shame and social disapproval, it is possible that stigmatization is even more damaging to narcissistic youth than to others.

What, then, should clinicians do when a young patient suffers from persistent narcissistic pathology to such an extent that these problems would meet the criteria for NPD diagnosis? We propose that they should weigh, for each individual patient, the potential benefits of such a diagnosis against the risk of stigmatization and potential other costs. NPD diagnosis is viable in individual cases when the benefits of appropriate treatment or disorder acknowledgement can reasonably be expected to outweigh the psychological burden that the NPD label might cause.

Associated Traits and Disorders and Differential Diagnosis

Narcissism entails a unique, empirically distinguishable pattern of personality functioning. Consistent with this reasoning, in a recent study (Westen, DeFife, Malone, & DiLallo, 2014), a factor analysis was conducted to identify naturally occurring personality groupings within a clinical sample of adolescents (13 to 18 years). The analysis yielded three higher-order factors (Internalizing, Externalizing, Borderline/Dysregulated), and 10 lower-level personality traits including narcissism (as part of the Externalizing spectrum). Subsequent validation analyses in an independent clinical sample of adolescents showed that narcissism was positively associated with observer-rated delinquent and aggressive behavior, but negatively associated with observer-rated withdrawal, anxiety, depression, and thought problems.

Yet, although narcissism has unique characteristics, it does share overlap with associated personality traits and mental disorders. Most prominent among them, in youth, are the traits of psychopathy and Machiavellianism, borderline personality disorder (BPD), and oppositional defiant disorder (ODD). In clinical settings, accurate diagnosis can be difficult, especially because narcissistic patients typically do not seek help for their core narcissistic traits but rather for the associated problems they experience (e.g., fear of negative evaluation, inability to sustain close relationships, difficulty to manage angry or aggressive impulses).

Psychopathy and Machiavellianism

The traits of narcissism, psychopathy, and Machiavellianism have collectively been labeled the Dark Triad of personality (Paulhus & Williams, 2002). The common core of the Dark Triad personality traits is a disagreeable interpersonal orientation, associated with a tendency toward self-promotion, superficial charm, and aggression (Barry et al, 2011; Paulhus & Williams, 2002). Despite this common core, narcissism is distinct from the other Dark Triad traits in a number of important ways.

Compared with psychopathy, narcissism is marked by different emotional predispositions. Youth holding psychopathic traits (especially those high in the callous-unemotional dimension of psychopathy), tend to be emotionally cold, shallow, and fearless. Youth holding narcissistic traits, by contrast, tend to experience emotional extremes (e.g., euphoria and pride interspersed with shame and humiliation), are highly emotionally reactive to both positive and negative events that are relevant to their self-views or public image (e.g., public successes or failures), and often actually express those emotions (Thomaes et al., 2011). One other main difference lies in the intentionality behind psychopathic and narcissistic youth's adversarial interpersonal behavior. Psychopathic youth are more likely to intentionally harm others, perhaps partially because harming others derives them pleasure or fulfillment. For narcissistic youth, harming others is not a goal in itself, but is collateral damage from their egocentric pursuit of individual goals, their attempts to turn the tables when they feel insulted by others, or their inconsiderate neglect of others' needs and concerns (Barry et al., 2011).

Machiavellianism may be even more closely associated with narcissism, yet an important distinction lies in the motives behind Machiavellianists' social behavior. Youth high in Machiavellianism typically pursue dominance and social power as a goal in itself (i.e., they strive to be on top of others), whereas narcissists pursue social power only as a means to build a desirable public image and get the positive attention that they need (i.e., they strive to be admired by others). Another important difference is that narcissists have overly positive, inflated views of themselves (e.g., they see themselves as more important and competent than others, even when they aren't), whereas Machiavellianists

have relatively realistic views of themselves (Paulhus & Williams, 2002).

Borderline Personality Disorder

NPD shares some overlap with other PDs, especially BPD. Differential diagnosis can be especially challenging in adolescence—a time when emotional instability and reactivity (characteristic of both NPD and BPD) is more normative than it is at other ages. NPD and BPD are similar in that they are both marked by emotional instability, overdependence upon others' attention, and difficulty with sustaining mutually satisfying interpersonal relationships. It may be especially difficult to distinguish more vulnerable forms of NPD, marked by high levels of interpersonal difficulty and distress, from BPD (Dickinson & Pincus, 2003). Narcissists are different, however, in the *kind* of attention that they need. Narcissists' primary social motive is to be admired, and so in their interactions they seek to be respected, applauded, or adored. The primary social motive of individuals with BPD is to not be abandoned, and so in their interactions they seek to be reassured of the closeness of their interpersonal bonds. One other difference is that narcissists engage less in interpersonal idealization and subsequent devaluation than do individuals with BPD, who tend to engage in black-and-white thinking about other people. In fact, narcissists rarely idealize others (with the possible exception of their adoration for certain heroes with whom they can identify or who serve as a self-enhancing role-model). Finally, compared with individuals with BPD, individuals with NPD tend to be less impulsive and self-destructive (e.g., they are less likely to injure themselves).

Oppositional Defiant Disorder

In late childhood and adolescence, NPD also shares some overlap with ODD. Differential diagnosis may be complicated because the features that both disorders have in common are the very features for which patients with these disorders tend to seek psychological help. That is, individuals with NPD and ODD may present with very similar problems when they enter treatment. In particular, both NPD and ODD are marked by hostile or resentful predispositions, a tendency to externalize blame for one's own mistakes or misbehaviors onto others, and an unwillingness to take up compliant or submissive social roles or to follow others' requests. Grandiose manifestations of NPD, marked by a dominant and hostile interpersonal orientation, may be especially difficult to distinguish from ODD. Narcissists are different, however, in that their hostile, vengeful predispositions are specifically triggered by situations in which their grandiose self-images are undermined, whereas individuals with ODD tend to be hostile and vengeful in response to a broader array of situations that involve frustration or authority conflict. Narcissists are also different in their craving for positive attention, which is not a typical feature of ODD. Finally, whereas ODD usually becomes evident before age 8, narcissism (or at least its core characteristics) typically emerges only after age 8, or even considerably later. The age at which problems have first emerged are important to consider when trying to tease NPD and ODD apart.

Intervening with Narcissism and Its Consequences: Clinical Approaches

How to intervene with narcissistic pathology in youth? Ideally, narcissism interventions would be based on a thorough empirical knowledge base of the etiology and development of narcissism, which would allow clinicians to target the factors critical to the causation and maintenance of narcissistic pathology. In addition, given timely identification, such knowledge would allow clinicians to start their interventions in those stages of development when narcissism and its underlying processes are most susceptible to change. Alas, we know relatively little of the factors that cause and maintain initial narcissistic development, or the developmental stages when narcissism is most malleable. Thus, up until today, clinicians face a choice of making do with the means available to them and directly targeting those conditions that impair the psychological adjustment of their narcissistic patients (rather than intervening with their causal or maintaining factors), or not to intervene at all. Understandably, most choose the first (e.g., Kernberg et al., 2000).

Typical clinical interventions are targeted at narcissistic youth's (1) limited skills to manage ego-threatening experiences, and (2) limited awareness or acknowledgment of the needs and concerns of other people. Clinicians face the challenge to carefully motivate narcissistic youth to engage in self-reflection, obtain self-insight, and strive for self-improvement, without activating the feelings of worthlessness or inferiority that are pervasively threatening to them. When narcissistic youth feel that their egos are threatened in treatment, their commitment to treatment might decrease (Beck, Freeman, & Davis, 2004). Another factor that may complicate treatment is that narcissists often lack a strong motivation to change. Narcissistic patients, particularly those with grandiose narcissistic problems, may be reluctant to acknowledge the inadequacies (that they themselves may consider signs of weakness)

that may cause or sustain their problems (e.g., Young, Klosko, & Weishaar, 2003).

Cognitive-Behavioral Intervention

Various techniques from cognitive-behavior therapy (CBT) programs can be adapted to the specific needs of narcissistic youth. Psychoeducation can be used to teach youths how fluctuations in their self-esteem are linked to how they feel and behave. Affect education can be used to help youths to be aware of and accurately identify how they feel in ego-relevant situations, and to use that awareness to guide their thought and behavior. In social skills training, narcissistic youths may learn alternative ways of reacting to ego threats besides rigidly externalizing blame or lashing out against others. Social skills training may also teach narcissistic youths to acknowledge other people's perspectives, and to wisely balance their own interests with those of others. Cognitive reframing techniques can be used to alter the interpretation of ego threats (e.g., by teaching youths that criticism or failure does not automatically imply that one is worthless), to make youths realize that they do not have to excel at everything to be able to hold a favorable public image, and more generally, to motivate them to become less invested with the pursuit of self-esteem. Yet purely cognitive techniques by themselves may be insufficient at motivating youths to become less preoccupied with building and buttressing self-esteem, especially because that preoccupation is strongly emotionally and motivationally driven. As such, narcissistic youths may benefit from the incorporation of interventions that address their emotions and motivations more directly, such as mindfulness interventions.

Mindfulness Intervention

Mindfulness interventions teach youths to adopt an open, nonjudgmental awareness of their thoughts and feelings in the present moment. Individuals differ in their natural predispositions to be mindful, but mindfulness skills can also be effectively cultivated, in youth as well as in adults (e.g., Burke, 2010). Rather than trying to alter thoughts and feelings, which is often the goal of cognitive techniques, mindfulness interventions seek to change the way people *deal* with their thoughts and feelings. Mindfulness is a promising technique for use with narcissistic patients, for several reasons. First, it helps youths to disengage from automatically occurring thoughts and feelings that can result in impulsive, maladaptive behavior (e.g., from the anger that leads to aggressive behavior, or from the shame that leads to defensive self-aggrandizement; Andersen et al., 2002). Second, it helps youths to become aware of the full breadth and intensity of their emotional experience, including their negative self-related emotional experience, in a way that promotes acceptance and reduces defensiveness (i.e., the tendency to repress feelings of shame and humiliation; Gilbert, 2007). Research has shown that mindfulness can be effective at overwriting previously learned stimulus-response associations, and may lead to the extinction of automatically triggered emotional reactions (Hölzel et al., 2011). Third, mindfulness training can be effective at quieting the ego—at making people less involved with creating and maintaining desirable self-images. Mindfulness teaches individuals to view their psychological experience as transient rather than static. Negative self-related thoughts and feelings become less threatening when they are seen as mere psychological events that dissipate after some time (Hölzel et al., 2011). Because many problems that narcissistic youth face are caused by impulsiveness, problematic emotion regulation, and the continuous pursuit of grandiose self-esteem, mindfulness interventions may be particularly well-suited to reduce narcissistic maladjustment.

Importantly, mindfulness interventions should not be confused with interventions that focus on raising self-esteem, such as by providing indiscriminate praise. Parents and teachers often target praise at those who seem to need it the most—children with low self-esteem. More specifically, they often praise children with low self-esteem for who they are as a person (e.g., You're great!) or in an inflated manner (e.g., You made an *incredibly* beautiful drawing!), in an attempt to raise these children's self-esteem. However, such praise inadvertently leads children with low self-esteem to avoid challenges and to feel ashamed in the face of failure (Brummelman, Thomaes, Orobio de Castro, et al., 2014; Brummelman, Thomaes, Overbeek, et al., 2014). Thus, although praise is often well-intended, person-directed and inflated praise can ironically backfire in the face of difficulty or failure (also see Kamins & Dweck, 1999). Moreover, although empirical evidence is lacking, some experts are concerned that interventions that focus on raising self-esteem might inadvertently cultivate inflated and narcissistic self-views in youth (Twenge, 2006). Mindfulness does not boost self-esteem, but fosters an accepting, self-compassionate stance that helps individuals tolerate their failures and inadequacies. Because narcissistic youth find it difficult to accept failure and imperfections, mindfulness techniques may provide a powerful tool to help them to become less vulnerable to ego threatening events.

Schema Therapy

Schema therapy is an integrative psychotherapeutic approach based on, among others, cognitive-behavioral, attachment, and emotion-focused traditions (Young et al., 2003), that may be well suited for use with narcissistic youth (Behary & Dieckmann, 2011; Kellogg & Young, 2006). One key assumption underlying schema therapy is that in response to childhood experiences in which basic needs were not met (e.g., due to parental overvaluation or lack of warmth), youth may develop maladaptive schemas—deeply entrenched, biased ways of thinking about oneself and one's interpersonal relationships—that impair healthy psychological adjustment (Young et al., 2003). These maladaptive schemas may come to form the root of a personality disorder. Narcissistic youth often hold schemas that, in schema-therapy terminology, are labeled entitlement (the schema that one is special, better than others, and entitled to privileges), unrelenting standards (the schema that one must continuously strive to excel), defectiveness/shame (the schema that one is flawed, inferior, and unlovable), and approval seeking (the schema that one needs recognition, applause, and admiration; Behary & Dieckmann, 2011; Young et al., 2003).

Schema interventions are aimed at changing patients' maladaptive schemas, primarily by helping patients to fulfil the needs that were thwarted in childhood. Initially, this happens within the confines of the therapeutic setting—for example, when parents of a narcissistic patient were cold or provided conditional love, the therapist emphatically seeks to create a therapeutic setting that is warm and unconditionally accepting. Emotion-focused techniques can be used to try to make painful childhood memories less upsetting. For example, imagery techniques allow patients to re-enact and restructure difficult childhood memories, while letter-writing techniques (that let patients write open, constructive letters to those who they feel have harmed them) allow patients to affirm their interpersonal needs. Cognitive techniques can be used to teach patients about their motives and feelings and their consequences (e.g., therapists may teach patients that their need for admiration compromises their ability to sustain close relationships), and to restructure harmful cognitions (e.g., therapists may use what-if techniques to explore with patients the worst things that would happen if they are not seen as perfect by others). In the final stage of schema interventions, patients are encouraged to practice what they have learned in the real world, outside of the therapeutic setting. For example, narcissistic patients who feel unable to sustain close relationships can be guided to form close relationships in which they pursue mutual affection rather than continuous admiration. Such positive real-world experiences may affirm patients' adaptive schemas, and thereby create an upward spiral of improvement. As such, these real-world experiences should help patients sustain initial therapeutic change.

Intervening with Narcissism and Its Consequences: A Basic Research Approach

Basic research in nonclinical samples has explored the psychological processes that can be altered to improve the functioning of individuals high in narcissistic traits (e.g., Finkel, Campbell, Buffardi, Kumashiro, & Rusbult, 2009; Thomaes, Bushman, Orobio de Castro, Cohen, et al., 2009). The goal of this research was not to provide ready-to-use intervention strategies. Rather, this research sought to illustrate how psychological processes can be influenced to decrease problematic narcissistic functioning, at least in the short term. As such, this basic research may inform clinical approaches to intervening with narcissism and its consequences.

This line of research has followed a rather straightforward but important set of principles that promises to be guiding for future work in this field. The first principle is to identity what psychological processes are involved in the causation or maintenance of narcissists' problematic functioning. Such knowledge should inform the design of well-targeted strategies to try to influence narcissistic maladjustment. The second principle is to experimentally manipulate the processes that cause or maintain narcissists' problematic functioning. These experimental procedures sometimes take the form of premature, explorative versions of intervention strategies as they may eventually be implemented in regular intervention.

Reducing Narcissistic Aggression

As an illustration, we detail a study that we conducted to try to reduce the aggressive behavior of youth high in narcissism (Thomaes, Bushman, Orobio de Castro, Cohen, et al., 2009). This study was based on the finding that narcissists, due to their vulnerable egos, often respond aggressively to ego-threatening experiences (e.g., Thomaes, Bushman, et al., 2008). We reasoned that, in theory, attempts that would succeed at reducing narcissists' sensitivity to ego threatening experiences should also reduce narcissists' inclination to behave aggressively. Social psychologists have explored experimental procedures to reduce the psychological impact of ego threatening experiences; the most prominent procedure is self-affirmation (or value affirmation; e.g., Cohen, Garcia, Apfel, & Master,

2006). Self-affirmation procedures allow people to reflect on their personally important values, such as self-defining skills or interests. Self-affirmation procedures reduce the impact of ego threat by making people realize that their worth as a person does not hinge upon one particular domain of functioning (Cohen et al., 2006).

In the study, adolescents first completed a measure of narcissistic traits (the Childhood Narcissism Scale), and then they were randomly assigned within their classrooms to either a self-affirmation or control condition. In the self-affirmation condition, they wrote about their most important values (e.g., being athletic, being creative, belonging to a social group, having good relationships with friends or family) and why these are important to them. In the control condition, they wrote about their least important values and why these may be important to others (for a detailed account of self-affirmation procedures, see Cohen et al., 2006). These exercises took about 15 minutes to complete. In the weeks following the self-affirmation manipulation, measures of aggressive behavior and experiences of ego threat were obtained. Specifically, aggression was measured using a peer nomination instrument that contained items for physical, direct verbal, and relational aggression. Experienced ego threat was measured by asking participants to rate how satisfied they were with themselves in the past week—lower ratings are reflective of higher levels of experienced ego threat.

The results showed that the self-affirmation manipulation reduced narcissistic aggression. In the control condition, the familiar pattern of results emerged with narcissists being more aggressive than others when they experienced high levels of ego threat. (This result is similar to what previous studies, such as Thomaes, Bushman, et al., 2008, have obtained in the laboratory.) Yet this familiar pattern of results was eliminated in the self-affirmation condition. Here, narcissists were no more aggressive than others, regardless of whether they had experienced high levels of ego threat. These results indicate that it is possible to reduce narcissistic aggression by making individuals less sensitive to ego threatening experiences. The results also indicate that seemingly minor manipulations, if they are targeted at the exact processes that cause or maintain narcissists' problems, can have sustained real-world effects.

Implications for Clinical Intervention

Basic research such as that described previously may have implications for clinical intervention. First, it illustrates that it is possible to reduce narcissists' problematic behaviors by implementing theory-based, well-targeted strategies to ameliorate the precise conditions and processes that normally drive these problematic behaviors. Second, basic research provides an empirical basis that may help clinicians to design interventions that target the factors that cause and maintain narcissists' problematic functioning.

That said, several important steps need to be taken to derive effective clinical intervention strategies based on the experimental procedures used in basic research. First, one challenge that clinicians face is to try to make intervention strategies effective for longer time periods. From a basic research perspective, the mere observation that certain experimental manipulations can cause improved functioning among narcissists is important by itself. From an applied perspective, it is more important that initial positive change in narcissists' functioning be sustained for a longer period of time. For example, in our study described above, the 15-minute self-affirmation exercise reduced narcissistic aggression for a period of a school week. A critical applied question is how the intervention effect can be sustained over time. One strategy might be to help patients incorporate effective exercises in their daily lives, such as by teaching them how to employ self-affirmation exercises in times of need.

Second, once potentially lasting intervention strategies have been devised, their effectiveness should be examined in applied or clinical settings. Thus far, research in this field has been conducted in laboratory or controlled field settings. These settings are ideal as a first step in the sequence of devising interventions because they allow for a relatively clean test of the presumed intervention effects. Yet, an important next step is to examine these intervention effects in less controlled applied or clinical settings. For example, researchers and practitioners might want to build on the Thomaes, Bushman, Orobio de Castro, Cohen, et al. (2009) study by incorporating self-affirmation procedures in their treatment of narcissistic individuals with aggressive behavior problems. In the most rigorous research design, patients would be randomly assigned to receive either treatment-as-usual or treatment-as-usual plus self-affirmation procedures, so that it could be examined what is gained by incorporating self-affirmation procedures in regular treatment. Another option might be to try to implement self-affirmation procedures in regularly employed conduct problem prevention or intervention programs in schools, and to examine what is gained in this way.

Conclusion

Clinicians and researchers increasingly recognize narcissistic maladjustment in youth, and are making progress at

trying to prevent narcissism and its consequences. In this section, we covered some key issues related to the diagnosis and treatment of narcissistic maladjustment in youth. We hope this section will spur future research on narcissistic pathology in youth, research that should further ease the burden that narcissistic youth place on themselves and the people around them.

CONTROVERSIES

A number of controversies and unanswered questions surround the topic of narcissism in youth. Three will be discussed here. First, there has been a somewhat polarized debate on whether societal levels of narcissism have been increasing over the past decades, with some authors claiming that it has (perhaps even to epidemic proportions; Twenge & Foster, 2008), and others challenging this claim on methodological grounds. Second, experts have differed in their views of the extent to which narcissism is adaptive, with some emphasizing that it may be beneficial for youth to hold at least some level of narcissism (particularly its leadership/authority features), and others emphasizing the harmful consequences of narcissism to both individuals themselves and the people around them. Third, there have been different views on what's behind the narcissistic mask, with some experts believing that narcissism is essentially a cover-up for deep-seated feelings of insecurity and insufficiency, and others arguing that narcissists have nothing to hide and are actually convinced of their exceptional talents and superiority over others.

Narcissism and Generational Change

Western culture has become increasingly individualistic over the past decades, perhaps especially from the 1960s or 1970s onward (e.g., Fukuyama, 1999). It seems plausible to assume that this cultural change has translated into the personality traits, self-evaluations, and behavioral predispositions of the individuals who make up society. Indeed, there is evidence to suggest that college students in the United States have come to score higher on agentic traits such as independence and assertiveness from the 1970s to the 1990s, and have come to evaluate themselves more positively on agentic traits such as the drive to achieve and leadership ability from the 1960s to 2009 (Twenge, Campbell, & Gentile, 2012). Also, there is evidence that college students as well as younger adolescents and preadolescents have come to hold increasingly high levels of self-esteem from the 1980s to the 1990s, and further up until 2008 (Gentile, Twenge, & Campbell, 2010). These patterns of psychological change over generations beg the question of whether levels of narcissism have also increased with the rise in individualism.

Evidence for Increases in Youth Narcissism Over the Past Decades

Jean Twenge and her colleagues have conducted cross-temporal meta-analyses and used other sources of historic evidence to conclude that today's young people are considerably more narcissistic than previous generations of young people. These authors have used time-lagged meta-analytic techniques, and compared narcissism levels in samples of people (in particular college students) of the same age at different historic periods. This technique allows for comparisons in level of narcissism across generations.

For an initial study, a systematic literature search yielded a total of 85 independent samples of college students from the United States who completed the NPI at some point in time between 1982 and 2006 ($N > 16{,}000$, 60% female; Twenge, Konrath, Foster, Campbell, & Bushman, 2008). When weighted by sample size (effect sizes obtained in larger samples were treated as more influential), there was a strong positive association ($\beta = .53$, $p < .001$) between NPI scores and year of data collection, such that more recent generations of college students reported higher levels of narcissism. In fact, as the authors noted, almost two-thirds of the most recent college students in their sample would have scored above the mean narcissism score two decades earlier. They also noted that the increase in narcissism was steady over time (there were no indications that narcissism had risen more steeply in some periods than in others), and tended to be stronger for women than for men.

An updated version of the meta-analysis, which included studies up until 2009 and, more importantly, controlled for possible confounding by campus (the possibility that historic differences in level of narcissism were not actually driven by year of data collection, but by differences in campus populations sampled at different points in time), found further support for increased levels of narcissism among American college students (Twenge & Foster, 2010). Other evidence from the same group of authors was not directly relevant to the question of whether narcissism has increased over time, but did suggest that it has become more common for Americans to strive for uniqueness and to stand out from the rest rather than to fit in with the crowd—developments which might be consistent with a more general trend toward individualistic self-focus. For example, an analysis of the first names given to 325 million American babies born 1880 to 2007 found that common

names have become increasingly less popular between the 1950s and 2007, even when controlling for immigration rate (Twenge, Abebe, & Cambell, 2010). Also, analysis of the words used in popular song lyrics suggests a historic trend toward word use indicative of a more individualistic self-focus (as evidenced by the use of first-person singular pronouns such as I or my) and less communal group focus (as evidenced by the use of first-person plural pronouns such as we and our) from 1980 to 2007 (DeWall, Pond, Campbell, & Twenge, 2011).

Together, this line of evidence is consistent with the view that with the rise of individualism from the second half of the previous century, Western young people have become increasingly narcissistic over time.

Evidence Against Increases in Youth Narcissism Over the Past Decades

Other authors, and Kali Trzesniewski and Brent Donnellan in particular, have been critical of the view that levels of narcissism have been increasing over time. In fact, they have argued that the empirical evidence on presumed generational change in narcissism, and interpretations in the media and some popular scientific writings (such as that the Western world is currently suffering from a "narcissism epidemic"), are much ado about nothing (Donnellan, Trzesniewski, & Robins, 2009; Trzesniewski, Donnellan, & Robins, 2008a, 2008b).

These authors have analyzed data from samples of University of California students from 1982 to 2007 and found no evidence for meaningful increases in narcissism (Donnellan, et al., 2009; Trzesniewski et al., 2008a, 2008b). These authors raised three methodological criticisms of research on the narcissism epidemic. First, they argued that all findings that point toward generational increases in narcissism have been obtained in convenience samples of college students, and that it is problematic to make inferences based on convenience samples about entire birth cohorts or trends in the general population. For example, it is possible that findings on generational change in narcissism reflect no actual societal trend but merely a change in the kinds of individuals who attend college or participate in psychological research in different periods in time.

Second, Trzesniewski et al. (2008b) argued that examining potential changes in narcissism as an overall construct—as Twenge and her colleagues have mainly done—is less informative than examining potential changes in individual facets of narcissism. The seemingly straightforward conclusion that levels of narcissism among youth have been increasing over the past decades may not be very informative if that increase was driven entirely by increases in some facets of narcissism, but not in others. Importantly, then, Trzesniewski et al. (2008b) found evidence to suggest that the superiority and vanity facets of narcissism have been slightly decreasing among American college students between 1996 and 2007, whereas the self-sufficiency facet has been slightly increasing over the same time period. This is especially relevant, they argue, in light of evidence that the superiority and vanity facets of narcissism might be more psychologically maladaptive than the self-sufficiency facet. If so, they argue, it would be premature to conclude that possible increases in narcissism may bring about interpersonal and societal problems.

Third, Trzesniewski et al. argue that cohort differences in psychological traits, such as narcissism, are only meaningful to the extent that it is possible to explain *why* certain sociohistorical developments lead to those cohort differences. Twenge and her colleagues did provide such an explanation, and suggested that increases in narcissism may be rooted in individualistic trends in Western society. In particular, they thought that the self-esteem movement, which has led to a preponderance of educational programs and media campaigns emphasizing the importance of feeling good about oneself over real accomplishment, may have cultivated increases in narcissism among American youth. Yet, Trzesniewski et al. pointed out that there is no evidence that self-esteem programs lead children to hold narcissistic or inflated self-views, which might render the individualism hypothesis for increases in narcissism premature.

Conclusion

What is needed to be able to draw a concluding statement on generational change in narcissism are representative cohort studies that include a standard measure of narcissism. Such studies are not available to date. As it stands, there is evidence from multiple sources that provide evidence to suggest that secular societal trends exist, yet the magnitude and toxic nature of these trends for the general population of American youth (let alone for other youth) is unknown.

Narcissism and Psychological Health

How problematic is it for individuals to hold narcissistic traits? Narcissism has been typically thought of by theorists and researchers as a primarily maladaptive trait. Indeed, narcissism is linked to emotional extremity, self-esteem instability, fear of being negatively evaluated by others, reduced perspective taking skills and empathic concern, an adversarial interpersonal orientation, and the

predisposition to behave aggressively (i.e., traits that may primarily harm others, but may ultimately boomerang and harm narcissists' own psychological health as well). Yet, the issue of how (mal)adaptive narcissism is more complex than it might initially seem. To be sure, there is no debate about the maladaptive nature of NPD. There is debate, however, about the maladaptive nature of trait narcissism (illustratively, trait narcissism is sometimes labeled normal narcissism; e.g., Sedikides, Rudich, Gregg, Kumashiro, & Rusbult, 2004). For example, it might be difficult to reconcile conceptualizations of narcissism as a maladaptive trait with evidence that some members of society who are often seen as particularly successful, including corporate and political leaders, tend to be high on narcissistic traits (Campbell, Hoffman, & Marchisio, 2011; Watts et al., 2013). As Kets de Vries and Miller (1984, quoted in Campbell et al., 2011, p. 272) argued: "Narcissistic personalities . . . are frequently encountered in top management position. Indeed it is only to be expected that many narcissistic people, with their need for power, prestige, glamour, eventually end up seeking leadership positions. Their sense of drama, their ability to manipulate others, their knack for establishing quick, superficial relationships serve them as well."

And even if one is not in top management position, one may experience at least some benefits from such narcissistic traits as self-reliance, interpersonal charm, and the appearance of authority. It is conceivable that narcissistic individuals, youth as much as adults, benefit from narcissistic traits when trying to establish social relationships or when performing in competitive contexts. There are two perspectives on the potentially adaptive nature of narcissistic traits: the adaptive tipping point perspective and the adaptive facet perspective.

The Adaptive Tipping Point Perspective

It is sometimes thought that although extremely high levels of narcissism may not bode well for individuals (or the people around them), very low levels of narcissism may do neither. The argument is that individuals should be able to experience some level of grandiosity, to feel comfortable with some degree of positive attention, and not become overwhelmed by too much concern over others' well-being to be able to show optimal psychological adjustment. For example, youths who feel reasonably, but not overly, confident about how their competencies measure up to those of others may often be better off than youths who are more modest or submissive. According to this view, there might be an adaptive tipping point along the narcissism dimension at which individuals function particularly well, suggesting that narcissism may not be linearly but curvilinearly related to several important psychological and behavioral outcomes.

Although intuitively plausible, empirical evidence has not been kind to this possibility thus far. In our own research, we have failed to find curvilinear relationships between narcissism and important outcome variables, including aggressive behavior, mood reactivity, and symptoms of anxiety or depression. Others have found no empirical support for curvilinear effects of narcissism either (Barry et al., 2007). Future research needs to more comprehensively explore the adaptive tipping point perspective, but as is stands, it seems reasonable to assume that narcissism is linearly related to important outcomes of psychological (mal)adjustment.

The Adaptive Facet Perspective

Even if narcissism, as a single dimension, is related to indices of psychological maladjustment, it is possible that certain *facets* of narcissism are more adaptive than others. There is some empirical evidence consistent with this notion. Psychometric research on the NPI, the most commonly used measure of trait narcissism in adults, has shown that it is sometimes useful to distinguish between a number of narcissism facets—some of which are more adaptive (or at least less maladaptive) than others (Corry, Davis Merritt, Mrug, & Pamp, 2008; Raskin & Terry, 1988). For example, although the predisposition to show off and to see oneself as entitled to special privileges (a facet of narcissism labeled exhibitionism/entitlement) may bring little good to individuals, the predisposition to see oneself as a leader and to strive for authority (a facet of narcissism labeled leadership/authority) might be more adaptive, perhaps especially in societies that emphasize the importance of such traits (Corry et al., 2008).

Psychometric research on the NPI for Children (Barry & Ansel, 2011; Barry et al., 2007) has found that it is possible to distinguish between two facets that the developers of the scale labeled adaptive narcissism (i.e., comprising traits related to self-sufficiency and authority) and maladaptive narcissism (i.e., comprising traits related to exhibitionism, exploitativeness, and entitlement). As the labels suggest, the adaptive narcissism facet is associated with a self-assured, easy-going interpersonal orientation and the ability to be noticed by other people. The maladaptive narcissism facet has a darker side, and is associated with callous-unemotional and adversarial interpersonal traits including the predisposition to engage in aggressive and delinquent behavior (Barry et al., 2007; Barry & Wallace, 2010; Barry & Ansel, 2011). Yet, the mere fact that the

adaptive facet of narcissism has a number of adaptive correlates is important, but does not by itself prove its adaptive nature. Future research will need to provide a comprehensive picture of its positive and negative outcomes across multiple domains and multiple contexts. Finally, and perhaps most important, future research will need to show that adaptive narcissism actually is a facet that is inherent to narcissism, and does not merely reflect adaptive traits that happen to be associated with narcissism but are not inherent to it, such as one's perceived competence (Brown et al., 2009). In summary, although it is well possible that narcissism encompasses traits that are primarily adaptive, given the current state of empirical evidence it seems too early to draw final conclusions.

Narcissism and Masked Insecurity

One longstanding view has held that narcissists' grandiosity may function as a façade to conceal their deep-seated feelings of insecurity and insufficiency. According to this mask model of narcissism, narcissists exhibit grandiosity and act as if they feel superior to others in an attempt to hide inner self-loathing—a view that can be traced back to psychoanalytic writings, especially those of Kohut. At first blush, there is much to be said for this hypothesis. If narcissists would genuinely feel positive about themselves, then why would they experience the need to shout from the rooftops that they are exceptional, and why would they crave continuous validation from other people? And if narcissists would genuinely believe in their own superiority, then why would they be so sensitive to slight criticisms or failures? It seems plausible that narcissists search for continuous validation and avoid criticism or failure because deep down inside they actually feel insecure and inferior. What does the empirical evidence say?

Unfortunately, research on the mask model of narcissism that involves children or adolescents is lacking. Thus, the question of whether early manifestations of narcissism may function to blanket children's feelings of insecurity and insufficiency remains unanswered. Research involving adult participants does exist, and provides a rather complex picture. One line of research has relied on measures, such as the Implicit Association Test, that index implicit self-views (Greenwald & Farnham, 2000). In particular, this line of research has explored the possibility that narcissists may hold positive self-views on an explicit (or conscious) level, and more negative self-views on an implicit (or nonconscious) level, but has found inconsistent results (reviewed by Bosson et al., 2008). One particularly insightful study (Campbell, Bosson, Goheen, Lakey, & Kernis, 2007) found that narcissists hold positive explicit and implicit self-views on indices of agency (i.e., traits that reflect extraversion and competence, and function to distinguish oneself from others); but more neutral explicit and implicit self-views on indices of communion (i.e., traits that reflect agreeableness and affection, and function to connect oneself with others). Thus, there is no compelling evidence that narcissists harbor insecurities of which they are not aware. If anything, this research suggests that narcissistic adults hold *imbalanced* self-views, and evaluate themselves positively on agentic traits and less positively (but not negatively) on communal traits.

Yet, it is still possible that narcissists report more positive explicit self-views than they actually hold, perhaps to convince themselves or others of their grandiosity. This possibility was recently explored (Myers & Zeigler-Hill, 2012). Adult participants first completed measures of narcissism and self-esteem, and then reported their self-esteem again under conditions in which they were motivated to tell the truth using a bogus pipeline procedure. Participants were attached to bogus lie-detecting physiological equipment during the self-esteem assessment. Half of the participants were told that the equipment was switched on; the other half were told that the equipment was switched off. Narcissistic participants in the bogus pipeline condition reported lower levels of self-esteem than those in the control condition. In fact, narcissistic participants in the bogus pipeline condition reported lower self-esteem than nonnarcissistic participants did. By contrast, nonnarcissists reported equal levels of self-esteem in both conditions. Thus, these results indicate that although narcissists may not harbor negative self-views they are unaware of, they may deliberately provide somewhat inflated ratings of how they view themselves, and may actually hold more negative self-views than they typically report using standard assessment procedures. Future research will need to explore the mask model of narcissism in younger participants, especially in pre- and young adolescents, to examine the possibility that narcissistic traits emerge to defend against unwanted feelings of insecurity or insufficiency.

CONCLUSION AND FUTURE RESEARCH

The field of research on youth narcissism is young. It is only from the turn of this century, when the first youth measures of trait narcissism were developed (Barry et al., 2003; Frick et al., 2000), that researchers were able to study narcissistic personality functioning in children and adolescents in

a systematic, standardized way. And they did: As reviewed in this chapter, multiple groups of researchers across the world have started to examine the nature, causes, and consequences of youth narcissism.

What explains the strong increase of interest in youth narcissism as a research focus? One likely explanation is that developmental researchers increasingly realize that the classic adagio that favorable self-regard is the cornerstone of healthy psychological adjustment holds merit, but only tells part of the story. The category of youth holding favorable self-regard appears to be a mixed bag, with some youth (i.e., those who hold accurate, well-balanced positive self-views) faring better than others (i.e., those who hold inflated, defensive positive self-views). Although trait narcissism probably is not entirely maladaptive, it does provide researchers a key construct to learn more about the problematic traits and behavioral consequences that may be associated with youths' favorable self-regard. One other explanation is that there is increasing societal concern that youth in individualized, Western cultures might have become more entitled and self-centered over the past decades. Obviously, adults' concerns or complaints about today's youth are of all times, yet in this case empirical research suggests that there might be some reason for concern.

The field of research on youth narcissism has made impressive progress over the past years. It has shown that trait narcissism can be identified and measured reliably and validly in older children and adolescents (Barry et al., 2003; Thomaes, Stegge, et al., 2008). It has shown that narcissism is different from, and even largely unrelated to self-esteem—narcissists are not necessarily satisfied with themselves, but they passionately pursue grandiose self-views, and seek to create favorable images in the eyes of others. It has found that narcissism in youth, much like narcissism in adults, can have grandiose manifestations (as evident in grandiose and entitled self-views, and the sense of superiority) as well as more vulnerable manifestations (as evident in brittle and unstable self-views, and negative emotional reactivity). Perhaps most important, it has found that narcissism is relevant to multiple domains of psychological adjustment. Narcissism predisposes youth to behave aggressively, especially when faced with ego threatening experiences. Narcissism influences youth to pursue agentic rather than communal social goals, and to strive for interpersonal dominance rather than interpersonal closeness. Narcissism leads youth to be hypervigilant to the appraisals of others, and to experience intense negative mood following negative interpersonal appraisal. Finally, narcissism puts youth, and especially those with lower self-esteem, at risk to develop symptoms of anxiety and depression.

Notwithstanding scientific progress, there is still much to be learned. We propose six broad and important directions for future research on youth narcissism. First, research is needed to understand the etiology and development of narcissism. This research should examine multiple (e.g., social-learning, psychoanalytic) perspectives on the socialization of narcissism, and should be guided by the principles of equifinality (i.e., different developmental pathways may lead to similar outcomes) and multifinality (i.e., similar developmental pathways may lead to different outcomes; Cicchetti & Rogosch, 1996). From a developmental psychopathology approach, the ultimate goal for this research is to uncover the interplay between multiple constitutional (e.g., temperament) and social factors (e.g., parenting) that influence the emergence and course of narcissistic development. We have proposed a diathesis–stress model that describes one potential developmental pathway to narcissism: High levels of approach temperament may interact with dysfunctional parenting practices, such as parental overvaluation or lack of warmth, to jointly influence the emergence of narcissism. Similarly, we have suggested that individual differences in avoidance temperament may influence early manifestations of narcissism in its grandiose or more vulnerable forms. Also, we have proposed that narcissism typically develops as a derailment of normal self-development, and may not become manifest before age 8. These hypotheses need to be tested empirically. Related important questions are to what extent early emerging narcissistic traits are predictive of individual differences in narcissism later in life (to what extent are individuals high in narcissistic traits at some point in childhood or adolescence predestined to become narcissistic as adults?), and to what extent some developmental stages may show normative increases and decreases in narcissism (is adolescence indeed a period when narcissism reaches a developmental high?). In addition, more needs to be learned about resilience in the context of narcissistic development (Luthar, Cicchetti, & Becker, 2000; Masten, 2001): Why do some youth not develop narcissistic traits despite exposure to risk factors, such as parental overvaluation, or resume normal self-development after initial narcissistic development? An improved understanding of resilience will contribute to our knowledge of the origins and nature of narcissism and may help in designing effective, targeted intervention. The study of the etiology and development of narcissism deserves priority in the upcoming years.

Second, research is needed to understand more about what youth narcissism exactly entails. We see particular

merit in research on the addiction model of narcissism. Can narcissism be seen as an addiction to others' esteem (e.g., others' attention, praise, and admiration), as the model suggests? One way to answer this question is by testing whether narcissism shares hallmarks of addiction—including cravings, tolerance, and withdrawal. Such knowledge will not only yield fundamental insight into the nature of narcissism, but will also raise intriguing questions from developmental and clinical perspectives. From a developmental perspective, does narcissism share genetic predispositions, developmental trajectories, and developmental outcomes with more familiar addictions? And from a clinical perspective, does the treatment of narcissistic pathology benefit from incorporating strategies central to the treatment of drug addiction? Given that addictions are relatively resistant to change, should one aim to prevent narcissism before it develops into a full-blown addiction, rather than to treat it afterward (much like it is easier to prevent than to treat more familiar addictions)? Hence, by testing the parallel between narcissism and addiction, future research promises to yield important insights into the nature, development, and treatment of narcissism.

Third, an interdisciplinary, multiple levels of analysis approach is needed to develop an integrative understanding of the development of trait narcissism and narcissistic pathology. Should we think of the difference between trait narcissism and narcissistic pathology as dimensional, reflecting individual differences in intensity and pervasiveness of symptoms or in the extent to which symptoms interfere with adjustment? Or are there perhaps more qualitative differences between trait narcissism and narcissistic pathology? If so, how do such qualitative differences develop over time? A related set of questions concern the psychological processes that explain derailment of normal self-development into narcissistic pathology, and conversely, the psychological processes that maintain normal self-development and prevent youth from developing narcissistic pathology. As mentioned before, the fields of research on trait narcissism and narcissistic pathology in youth have remained largely separated thus far. Current conceptualizations of normal and pathological narcissistic personality functioning are diffuse and tell little about the fine line that runs between them. Accurate conceptualizations not only are relevant from a basic research perspective but also are necessary to inform discussions on dimensional versus categorical approaches to diagnosing narcissistic pathology (e.g., Miller & Campbell, 2008). A developmental psychopathology approach to narcissism, an approach which seeks to explain the processes underlying normal and abnormal development across the lifespan, and which examines psychopathological processes as deviations from normal development, provides a promising means to reduce the dualism in our understanding of trait narcissism and narcissistic pathology (Cicchetti & Toth, 2009; Sroufe, 1990).

Fourth, research is needed to inform developmentally tailored interventions to reduce the problematic manifestations or consequences of narcissism (regardless of whether these can be seen as reflecting pathology). Increased understanding of the psychological processes that explain problematic manifestations of narcissism is important to design novel intervention techniques. By testing the impact of theory-based procedures (such as self-affirmation procedures) on problematic narcissistic outcomes (such as narcissistic aggression) in controlled field settings, such basic research can lay the groundwork for narcissism interventions in less controlled clinical settings. A number of questions seem especially important. How can intervention techniques that are proven effective in laboratory or other controlled settings be adapted and implemented in clinical settings? How can intervention techniques that are proven effective on the group level, be tailored to fit the narcissistic problems that individual patients suffer from? Also, in what developmental phases are narcissists most likely to reap the benefits of intervention? Most basic research examines only the short-term impact of putative intervention techniques. Yet actual intervention obviously seeks to cause longer-term, or even self-sustaining reductions in narcissistic pathology. The overarching goal of intervention research would be to develop a knowledge base of intervention techniques that can be employed to treat specific manifestations or consequences of narcissism in developmental phases when change is most likely to occur. Once such well-targeted and developmentally sensitive intervention techniques have been tested in controlled field settings, they should be implemented in real-world contexts in collaborative efforts with practitioners and policy makers to benefit vulnerable youth and their families at a larger scale.

Fifth, research is needed to uncover the potential functions or benefits of trait narcissism. Researchers, clinicians, and laypeople alike have asked themselves whether narcissism is mainly a curse or a blessing. Obviously, there is no single answer to this question. Some narcissistic traits are more adaptive than others, and their adaptiveness may well differ between developmental phases and across contexts. Thus, relevant questions to be addressed are: Are certain narcissistic traits more adaptive than other

traits? Does the adaptiveness of these traits change over the course of development? For example, it seems plausible that it is functional for adolescents to adopt a narrow self-focus in the process of developing an autonomous identity, but that such a self-focus may be less functional for young adults when seeking to develop and maintain longstanding intimate relationships. And does the adaptiveness of narcissistic traits depend on social context? For example, a sense of entitlement might help children thrive in settings where resources are scarce (e.g., when they need to be able to assertively act in their self-interest), but might harm children's peer relationships in settings where resources are abundant. In summary, an important task for future research is to uncover when and why narcissism is a blessing or a curse.

Sixth, more research is needed on ethnic and cross-cultural differences in narcissism. The degree to which individuals feel part of a particular social group is an important aspect of their sense of self (Tajfel, 1981). Initial research on ethnic differences has suggested that, within the United States, Black adolescents tend be somewhat more narcissistic than are White adolescents, especially to the extent that they hold a strong sense of ethnic identity (Pickard, Barry, Wallace, & Zeigler-Hill, 2013). Future research should seek to understand the psychological processes by which youths' ethnic identity influences the development of narcissistic traits. This research may be guided by the principles of social identity theory (Tajfel, 2010), which suggests that the experience of being a minority group member may impact how individuals compare themselves to others (with minority members being more likely to engage in social comparisons within their own group), and how individuals attribute negative outcomes (with minority group members being more likely to make external rather than internal attributions); processes that might translate into ethnic differences in narcissism. Furthermore, in terms of cross-cultural research, it is often believed that narcissism should be higher in individualistic cultures than in nonindividualistic cultures. Although cross-cultural research on youth narcissism is lacking, one study involving mainly adults found that narcissism levels are higher in individualistic countries (United States, Canada, Western European countries) than in nonindividualistic countries (countries in Asia and the Middle East; Foster et al., 2003). Apart from cultural differences in individualism, differences in how strongly cultures emphasize honor (Leung & Cohen, 2011) might be relevant to narcissism as well. What is needed is systematic research on youth narcissism in representative samples of cultural groups across the world.

Coda

The study of youth narcissism has gained momentum over the past years. For a long time, the fields of developmental psychology and developmental psychopathology have been fascinated by the self. A new branch of this fascination now revolves around youth narcissism. We propose that the study of youth narcissism is important to these fields, in that it promises to yield a more accurate and comprehensive understanding of both normal and pathological self-development. By studying youth narcissism, researchers will be able to learn more about the multifaceted nature of the developing self. Moreover, they will be able to learn more about how healthy and less healthy forms of favorable self-regard develop, and how they can be distinguished from one another. The study of youth narcissism would benefit from an interdisciplinary approach to learn more about what narcissism essentially is, how it originates and develops, and how normal narcissistic traits should be distinguished from narcissistic pathology. We are looking forward to learning about the exciting new insights that will result from such a collaborative endeavor.

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CHAPTER 17

A Multilevel Perspective on the Development of Borderline Personality Disorder

PETER FONAGY and PATRICK LUYTEN

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INTRODUCTION

This chapter provides an update on the mentalizing approach to borderline personality disorder (BPD), which was originally formulated in the 1980s but has developed considerably over the past few years. The recent evolution of thinking on mentalizing has in particular been influenced by new findings in developmental psychology and psychopathology, the neurosciences, and the continuing experiences with the different varieties of the empirically evaluated treatment modality that evolved from this approach, mentalization-based treatment (MBT).

Accordingly, we present here a multilevel approach to BPD from a mentalizing perspective, integrating findings from clinical and developmental psychology as well as from the biological processes involved in BPD, which range from genetic to neurobiological, neuroendocrine and neural. Further, we adopt a life span perspective, discussing the emergence of BPD from infancy to adolescence and (young) adulthood. Adolescence in particular has been neglected in earlier research; we argue here that this stage of life is pivotal to understanding the origins of BPD.

The chapter is structured as follows. First, we briefly discuss the nature, prevalence, and core features of BPD. Specifically, we argue that any theoretical approach needs to facilitate our understanding of these core features, and particularly the subjective experience of individuals suffering from this disorder. Second, we provide a summary of the mentalizing approach to BPD, with an emphasis on the impairments in several dimensions of mentalizing that we consider typical of individuals with BPD. Next, we present a developmental psychopathology model of BPD, locating the origins of the mentalizing impairments typical of BPD patients in attachment disruptions. This also includes a discussion of the importance of gene–environment transactions in BPD, and an outline of emerging research findings concerning the neurobiology of BPD and the neural circuits involved in impairments in several dimensions of mentalizing in these patients.

[1]Color version of Figure 17.1 is available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

We close this chapter with an outline of MBT for BPD, and we present a new view on the mechanisms of change in the treatment of BPD, and suggest that this mechanism may be the missing link that connects and is shared by all effective treatments of BPD.

WHAT IS BORDERLINE PERSONALITY DISORDER?

The definition of BPD has been revised with each edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) in the direction of increasing specificity, to arrive at the current criteria requiring five out of the following nine features: (1) a pattern of unstable intense relationships; (2) inappropriate, intense anger; (3) frantic efforts to avoid abandonment; (4) affective instability; (5) impulsive actions; (6) recurrent self-harm and suicidality; (7) chronic feelings of emptiness or boredom (dysphoria); (8) transient, stress-related paranoid thoughts; and (9) identity disturbance and severe dissociative symptoms (American Psychiatric Association, 2000).[2]

The group of patients captured by the *DSM* BPD criteria is extremely heterogeneous. The dismantling of this heterogeneity is a major task facing the field. Understanding and untangling borderline heterogeneity is necessary to enable us to describe the domains of the pathology that are likely to have different etiological roots, and to describe and appropriately refine treatments to fit the various domains of pathology currently nested under the wide borderline construct. It is most unlikely that the numerous available evidence-based treatments are equally applicable to all subtypes of BPD. To be able to make a nuanced set of recommendations about what works for whom, it may be helpful to understand the origins of the concept of borderline, as the current usage of the term tends to focus on a limited, albeit important, subgroup of individuals with borderline features. We have reviewed these classical theories elsewhere (Higgitt & Fonagy, 1992).

A Little Phenomenology

Borderline personality disorder defined as outlined previously is a severe condition with a lifetime prevalence estimated at possibly as much as 6% (Grant et al., 2008). BPD is often comorbid with mood disorders (Sjastad, Grawe, & Egeland, 2012), anxiety disorders (Friborg, Martinussen, Kaiser, Overgard, & Rosenvinge, 2013), bipolar disorder (Perugi et al., 2013), and schizotypal and narcissistic personality disorders (PDs) (Tomko, Trull, Wood, & Sher, 2014). It may be particularly common in outpatient (Korzekwa, Dell, Links, Thabane, & Webb, 2008) and forensic (Slade & Forrester, 2013) populations, where between one-quarter and one-third may be expected to meet criteria for the diagnosis.

There is increasing consensus that BPD, as defined in *DSM-IV*, consists of three related core features. First, according to Linehan's theory (Linehan, 1993) and recent research (Crowell, Beauchaine, & Linehan, 2009; Glenn & Klonsky, 2009), *emotional dysregulation* is thought to drive other BPD symptoms. Experimental studies have indeed confirmed that patients with a BPD diagnosis are less willing to experience distress to pursue goal-directed behavior (Gratz, Rosenthal, Tull, Lejuez, & Gunderson, 2006; Salsman & Linehan, 2012), have significantly prolonged anger reactions (Jacob et al., 2008), show a reduced inhibition of negative emotional material (Domes et al., 2006; Gratz, Breetz, & Tull, 2010), manifest abnormalities in processing unpleasant emotional stimuli (Baer, Peters, Eisenlohr-Moul, Geiger, & Sauer, 2012; Hazlett et al., 2007), and are more likely to behave impulsively when in a negative mood (Chapman, Leung, & Lynch, 2008). Over any specific time period they are likely to experience dramatic shifts in mood states, manifest greater intraindividual variability in affect valence and intensity (Reich, Zanarini, & Fitzmaurice, 2012; Santangelo, Bohus, & Ebner-Priemer, 2012), and undergo heart rate increases not associated with metabolic activity (Reisch, Ebner-Priemer, Tschacher, Bohus, & Linehan, 2008; Trull et al., 2008). BPD patients also report more complex emotions, and experience greater problems in identifying specific emotions associated with higher levels of distress (Bornovalova, Matusiewicz, & Rojas, 2011; Ebner-Priemer et al., 2008; Preissler, Dziobek, Ritter, Heekeren, & Roepke, 2010), although this may be the effect rather than the cause of emotional hyperreactivity (Domes, Schulze, & Herpertz, 2009). Taking these pieces of evidence together, it is generally assumed that an anomalous reciprocal relationship between brain mechanisms underpinning the subjective experience of emotion (i.e., limbic structures) and mechanisms responsible for their regulation (i.e., anterior brain regions) brings about an aberrant processing of negative emotionality in patients with BPD (Maurex et al., 2010; Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013). However, it should be noted that some studies report no

[2] *DSM-5* has not changed the definition of any personality disorder diagnoses from those in *DSM-IV* because of opposition to the particular combination of trait measures and clinical methods suggested (Shedler et al., 2011), although a new model informed by the draft recommendations is included as part of Section III of *DSM-5*.

differences in emotional response to affect-eliciting stimuli in BPD patients (Herpertz, Dietrich, et al., 2001; Herpertz, Kunert, Schwenger, & Sass, 1999; Herpertz et al., 2000; Suvak et al., 2012), which, as we shall see, reflects the complexities involved in examining emotional dysregulation in BPD outside a genuine social context.

Second, BPD is characterized by *impulsivity*, the most disquieting aspect of which is suicidality. Three-quarters of BPD patients attempt suicide at least once (Black, Blum, Pfohl, & Hale, 2004). While outpatient treatment appears at least in some studies to decrease suicide attempts, medication visits appear to increase them (Soloff & Fabio, 2008). Affective instability, particularly negative mood amplitude and the intensity of negative mood (Links, Eynan, Heisel, & Nisenbaum, 2008), has been associated with an increased likelihood of impulsivity (Gratz et al., 2010). A diagnosis of major depressive disorder (MDD), substance use disorder (SUD), posttraumatic stress disorder (PTSD), the presence of self-harm, adult sexual assault, having a caregiver who has completed suicide, affective instability, and more severe dissociation have each been shown to increase suicidal behavior (Wedig, Frankenburg, Bradford Reich, Fitzmaurice, & Zanarini, 2013; Wedig et al., 2012). A curious aspect of the impulsivity literature in BPD is that while self-report measures point to high levels of impulsivity (e.g., Domes et al., 2006; Grootens et al., 2008), behavioral measures such as the go/no-go task (e.g., Jacob et al., 2010; Lampe et al., 2007) less readily demonstrate inhibition problems in laboratory settings. It is possible that the impulsivity observed in self-report is more closely related to an incapacity to inhibit mental states (cognitive inhibition), and it is unruly mental states that go on to generate problem behaviors. Suicide risk has been associated with poor social adjustment and the absence of supporting family, work, and social relationships (Soloff & Fabio, 2008; Soloff, Feske, & Fabio, 2008; Wedig et al., 2013; Wedig et al., 2012).

Indeed, *social dysfunction* is typically seen as the third factor in the core triad of BPD symptom clusters, and specific dysfunctions within and across interpersonal domains have been invoked to account for the origins and maintenance of BPD (e.g., Gunderson, 2011; Hill et al., 2008; Soeteman, Verheul, & Busschbach, 2008; Tomko et al., 2014). For example, patients with BPD experience heightened social problem-solving difficulties compared with other clinical groups (Dixon-Gordon, Chapman, Lovasz, & Walters, 2011; Maurex et al., 2010; Thoma, Friedmann, & Suchan, 2013) and report high levels of disturbances in romantic relationships (e.g., Bhatia, Davila, Eubanks-Carter, & Burckell, 2013; Clifton, Pilkonis, & McCarty, 2007; Hill et al., 2011). While certain social problem-solving deficits may be linked to impulsivity (McMurran & Wilmington, 2007), they could equally be secondary to an autobiographical memory deficit (Maurex et al., 2010). Social problem solving is also likely to be directly connected to dysfunctional attachment processes, which, as evidence we will discuss further below shows, have long been considered to characterize this group (Agrawal, Gunderson, Holmes, & Lyons-Ruth, 2004; Barone, Fossati, & Guiducci, 2011; Fonagy et al., 1996; Gunderson, 1996; Levy, 2005; Levy, Meehan, Weber, Reynoso, & Clarkin, 2005; Minzenberg, Poole, & Vinogradov, 2006a; Patrick, Hobson, Castle, Howard, & Maughan, 1994; Rosenstein & Horowitz, 1996; Steele & Siever, 2010; Stovall-McClough & Cloitre, 2003). In one study of a sample of patients with BPD (Fonagy et al., 1996), which controlled for conditions that commonly co-occur with BPD, a unique association between BPD and preoccupied attachment was reported (75% of PD patients meeting criteria for BPD fell into the rarely used adult attachment scoring subgroup of fearfully preoccupied with respect to trauma), even after controlling for comorbid Axis I and II disorders. Numerous studies have reported that individuals with BPD appear to anxiously expect, readily perceive, and intensely react to social rejection (Ayduk et al., 2008; Berenson, Downey, Rafaeli, Coifman, & Paquin, 2011; Renneberg et al., 2012). We, along with many others, have highlighted a characteristic pattern in borderline patients of fearful attachment (attachment anxiety and relational avoidance), painful intolerance of aloneness, a marked hypersensitivity to social situations, alertness to a hostile response from others, and greatly reduced positive memories of dyadic interactions (e.g., Berenson et al., 2011; Bhatia et al., 2013; Chapman, Walters, & Dixon Gordon, 2014; Critchfield, Levy, Clarkin, & Kernberg, 2008; Dixon-Gordon, Gratz, Breetz, & Tull, 2013; Frick et al., 2012; Gratz et al., 2010; Gunderson & Lyons-Ruth, 2008; Miano, Fertuck, Arntz, & Stanley, 2013; Preissler et al., 2010; Staebler, Helbing, Rosenbach, & Renneberg, 2011). Similarly, Beck, Freeman, and Davis (2004) proposed that the prototypical pattern of alternately clinging and pushing people away is underpinned by a feeling of helplessness in the absence of constant support of others, combined with a profound mistrust of others. Lack of trust also predicts suicide (Bhar, Brown, & Beck, 2008; Ozkan & Altindag, 2005) and could be related to the rejection sensitivity trait that frequently prompts dissociation and self-injurious behavior triggered by aversive interpersonal events (Gratz et al., 2006; Gunderson, 2007; Zanarini, Laudate, Frankenburg, Wedig, & Fitzmaurice, 2013). Rejection sensitivity, in turn,

may be mediated by lack of affect regulation capacity (Dixon-Gordon et al., 2013), which serves to exaggerate the experience of social rejection.

The interrelatedness of these primary deficits once again highlights the need for a developmental psychopathology model that maps the interactions between, and the developmentally changing prominence of, a range of genetically programmed or environmentally triggered influences on individual function.

Further, in our opinion, three features of BPD that refer to disturbances in social relatedness continue to be underemphasized but are essential to a comprehensive developmental understanding of BPD, as well as a full appreciation of the subjective experience of patients with the disorder, and are central in the MBT approach to BPD:

1. First, *dissociative comorbidity* is more frequently reported by patients with BPD than other groups (Barnow et al., 2012; Ross, 2007; Zanarini, Frankenburg, Jager-Hyman, Reich, & Fitzmaurice, 2008). It appears to be a response to increased stress (Stiglmayr et al., 2008); to be associated with emotional neglect (Sar, Akyuz, Kugu, Ozturk, & Ertem-Vehid, 2006); to moderate emotional responsivity (Barnow et al., 2012); to be linked to suicidal ideation (Klonsky, 2008); and to reduce the likelihood of effective psychosocial treatment (Kleindienst et al., 2011).

2. Second, a *disturbed sense of identity*, or "failure to establish stable and integrated representations of self and others" (Livesley, 2003, p. 19), is frequently described as characteristic of BPD (e.g., Blatt & Auerbach, 1988; Bradley & Westen, 2005; Jorgensen, 2010; Kernberg, 1975, 1984). Rooted in a dysfunction or deficit of a sense of agency or self-directedness, this characteristic has been identified in empirical clinical studies (e.g., Adler, Chin, Kolisetty, & Oltmanns, 2012; Barnow, Ruge, Spitzer, & Freyberger, 2005; Bender & Skodol, 2007; Jorgensen et al., 2012).

3. Third is the experience of intense *inner pain* that is out of keeping with the significance of the event. This may indeed be a core feature of BPD (Zanarini & Frankenburg, 2007), and is frequently associated with disturbed relationships (Gunderson & Lyons-Ruth, 2008) and childhood abuse and neglect (Holm & Severinsson, 2008; Hopwood & Zanarini, 2012). It is commonly prompted by social situations that involve rejection, abandonment, or isolation (e.g., Briand-Malenfant, Lecours, & Deschenaux, 2012; Hopwood, Thomas, & Zanarini, 2012; Stiglmayr et al., 2008); it involves intense or toxic shame (Gratz et al., 2010; Levy, Edell, & McGlashan, 2007; Rusch et al., 2007), and can prompt dissociation (Philipsen et al., 2004) and self-harm (Coid, 1993; Wedig et al., 2013; Zanarini, Laudate, Frankenburg, Reich, & Fitzmaurice, 2011; Zanarini et al., 2013). A number of clinicians have described the phenomenological intensity of this experience, but Gunderson and Lyons-Ruth (2008) drew attention to the interpersonal hypersensitive phenotype and made it a central part of any account of BPD; certainly, recovery is associated with improvements in this respect (Reed, Fitzmaurice, & Zanarini, 2012).

KEY IDEAS IN THE MENTALIZATION-BASED APPROACH TO BPD

The mentalizing approach aims to provide a comprehensive theoretical account of the phenomenology and origins of BPD from a developmental psychopathology perspective. This is congruent with increasing interest, over recent years, in the emergence of BPD (Arens et al., 2013; Bornovalova, Hicks, Iacono, & McGue, 2013; Chanen & McCutcheon, 2013; Stepp, Olino, Klein, Seeley, & Lewinsohn, 2013), particularly as there is increasing evidence to suggest that the disorder may have roots in early development (Goodman, Patel, Oakes, Matho, & Triebwasser, 2013; Lopez-Castroman et al., 2013; Perroud et al., 2013; Siever, 2008).

Here we first briefly summarize the key assumptions of the mentalizing approach to BPD; each of these assumptions will subsequently be discussed in detail (see Allen, Fonagy, & Bateman, 2008; Fonagy & Luyten, 2009; Fonagy, Luyten, & Strathearn, 2011).

Developmental Perspective

A developmental perspective is at the heart of the mentalizing approach to BPD. The mentalization model was first outlined in the context of a large empirical study in which security of infant attachment with parents proved to be strongly predicted not only by the parents' security of attachment during pregnancy (Fonagy, Steele, Steele, Moran, & Higgitt, 1991) but also even more by the parents' capacity to understand their childhood relationships with their own parents in terms of states of mind (Fonagy et al., 1991).

This study paved the way for a systematic program of research demonstrating that the capacity to mentalize, which emerges in the context of early attachment relationships, is a key determinant of self-organization and affect regulation. The concept of mentalization postulates that one's understanding of others depends on whether

one's own mental states were adequately understood by caring, attentive, nonthreatening adults. Problems in affect regulation, attentional control, and self-control stemming from dysfunctional attachment relationships (Agrawal et al., 2004; Lyons-Ruth, Yellin, Melnick, & Atwood, 2005; Sroufe, Egeland, Carlson, & Collins, 2005) are thus thought to be mediated through a failure to develop a robust mentalizing capacity (Bateman & Fonagy, 2010). From this perspective, mental disorders in general can be seen as the mind misinterpreting its own experience of itself, and therefore of others (Bateman & Fonagy, 2010).

Mentalizing thus refers to the understanding of both the self and others in terms of thoughts, feelings, wishes, and desires. This capacity is not a constitutional given but does seem to be a capacity that is in part prewired (Kovacs, Teglas, & Endress, 2010). It might be useful to understand it as being, just like language, based on an evolutionarily protected, nonconscious, reflexive appreciation of others' intentions, emotions, and perspectives (Seyfarth & Cheney, 2013), which is subject to modulation by social environments. Verbal competence may be guaranteed by our genes, but the quality of an individual's command of a language is down to the exigencies of geographical and social origin influencing developmental achievements over the early years of life. The development of mentalizing is thus similarly thought to depend on the quality of the social learning environment, the child's family relationships, and, in particular, early attachments, as the latter reflect the extent to which the child's subjective experiences were adequately mirrored by a trusted other. The attachment figure's ability to respond with contingent and marked affective displays of their own experience in response to the infant's subjective experience makes possible the child's development of coherent second-order representations of these subjective experiences. As we will discuss in more detail below, we are thus not adopting a naive environmentalist perspective on BPD. Rather, the interaction between genetic predisposition and early and later influences on the development of the capacity to mentalize is thought to be crucially important in the development of BPD.

Mentalizing and the Development of Self-Regulation and Control

Specifically, we believe that the quality of affect mirroring by attachment figures plays a major role in the development of affect-regulatory processes and self-control (including attention mechanisms and effortful control) as well as the capacity for mentalizing in the individual. Mentalizing is seen as a fundamentally bidirectional or transactional social process (Fonagy & Target, 1997): it is thought to develop in the context of interactions with others, and its quality in relation to understanding others is assumed to be influenced by how well those around us mentalize. This experience of how other people mentalize is internalized, enabling us to enhance our own capacity for empathizing and to better engage in interactive social processes; conversely, poor mentalizing begets poor mentalizing.

The Multidimensional Nature of Mentalizing

The quality of mentalizing may be conceptualized as the achievement of a balance between the two extremes of four dimensions, each with their own relatively distinct underlying neural circuits (Fonagy & Luyten, 2009). These four dimensions are (1) cognitive versus affective mentalizing; (2) mentalizing based on external versus internal features of self and others; (3) automatic versus controlled mentalizing; and (4) mentalizing with regard to self versus others.

Automatic mentalizing describes fast, parallel, reflexive processes that require little consciousness or effort, while *controlled* mentalizing involves more conscious, deliberate, serial reflective processes. The focus of mentalizing can be the *self* (including one's embodied experiences) or *others*, and mentalizing can involve inferences based on the *external* features of others (e.g., their facial expressions) or assumptions about *internal* features—that is, one's own mind or that of others. Finally, full mentalizing involves the integration of both *cognitive* knowledge (i.e., agent-attitude propositions) and *affective* input (i.e., affective-state propositions; see later in this chapter for a fuller description). From this perspective, different types of psychopathology can be distinguished on the basis of different combinations of impairments along these four dimensions (which we can refer to as different *mentalizing profiles*; see Figure 17.1 for an example of the mentalizing profile in BPD).

The Context/Relationship-Specific Nature of Mentalizing

The capacity to mentalize has both trait and state aspects that may vary in quality in relation to emotional arousal and the interpersonal context (e.g., mentalizing levels may differ considerably when reflecting on the relationship with one's mother vs. one's father, for instance, or when reflecting offline on these relationships versus online in the course of real-life interactions).

Typically, with heightened psychological arousal, the capacity for controlled mentalizing is increasingly lost, and automatic and often unreflective mentalizing starts

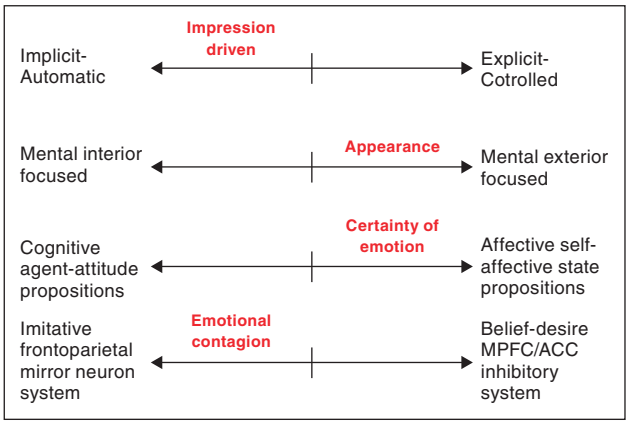


Figure 17.1 Mentalizing profile of the prototypical BPD patient. See footnote 1.

to dominate (Figure 17.2). Attachment hyperactivating and deactivating strategies play a key role in explaining the relationships among stress/arousal and mentalizing in different arousal/interpersonal contexts.

The Reemergence of Nonmentalizing Modes

The capacity for mentalizing and the associated capacities for affect representation, affect regulation, and attentional control normally obscure forms of experiencing subjectivity that developmentally antedate the capacity for full mentalizing. These modes of experiencing the self and others tend to reemerge whenever we lose the ability to mentalize, as typically happens in individuals with BPD, particularly in high arousal contexts:

In the *psychic equivalence mode*, thoughts and feelings become too real, and there are no conceivable alternative perspectives. There is a suspension of doubt, and the individual increasingly believes that his or her own perspective is the only one possible.

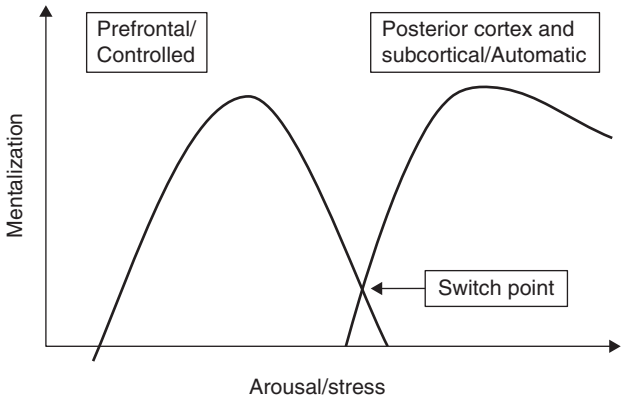


Figure 17.2 A biobehavioral switch model of the relationship between stress and controlled versus automatic mentalization.

Second, in the *teleological mode* there is only a recognition of real, observable goal-directed behavior and objectively discernible events that may potentially constrain these goals. Hence, the individual can recognize the existence and potential role of mental states, but this recognition is limited to very concrete, observable goals.

Third, in the *pretend mode* thoughts and feelings become severed from reality (which we term hypermentalizing or pseudomentalizing); in the extreme, this may lead to feelings of derealization and dissociation.

These three prementalizing modes are particularly important as they are often accompanied by a pressure to externalize unmentalized aspects of the self (so-called *alien-self parts*), which may be expressed in attempts to dominate the mind of others, self-harm, or other types of behavior that in the teleological mode are expected to relieve tension and arousal, a feature typical of BPD (Fonagy & Target, 2000).

Mentalizing and Pathology of the Self

Impairments in mentalizing are thought to play an important role in the emergence of various psychiatric disorders that involve pathology of the self (Sharp, Fonagy, & Goodyer, 2008) and thus are not limited to BPD (Bateman & Fonagy, 2004; Fonagy et al., 2010). Indeed, mentalizing impairments can be thought of as a transdiagnostic vulnerability factor that is implicated in a wide variety of disorders, ranging from antisocial PD (Bateman, Bolton, & Fonagy, 2013; Bateman & Fonagy, 2008b; McGauley, Yakeley, Williams, & Bateman, 2011) to eating disorders (Cate, Khademi, Judd, & Miller, 2013; Rothschild-Yakar, Levy-Shiff, Fridman-Balaban, Gur, & Stein, 2010; Skårderud, 2007a, 2007b), PTSD (Allen et al., 2008), depression (Luyten, Fonagy, Lemma, & Target, 2012), and functional somatic disorders (Luyten, van Houdenhove, Lemma, Target, & Fonagy, 2012).

In subsequent sections, we discuss these assumptions in more detail, focusing on BPD. Yet, inevitably, in accordance with the developmental psychopathology approach, this will also lead us to discuss overlap between BPD and related disorders that share important developmental trajectories with BPD.

ATTACHMENT, MENTALIZING, AND BPD

As noted, the mentalizing approach to BPD is fundamentally developmental. Its focus is on attachment disruptions and related impairments in mentalizing or the capacity to

develop second-order representations (representations of representations). Yet we are quite aware that this focus may lead to a theory that is overdetermined. We seek to situate these ideas, therefore, within a broader developmental approach that emphasizes the elements of interaction and diathesis–stress that are implicated in the emergence of BPD. In this section, we elaborate on how the most current thinking on mentalizing is informed by and theoretically congruent with this increasingly nuanced and complex picture of the developmental processes in BPD and the emerging evidence for gene–environment transactions.

The developmental theory we advance has several subhypotheses. First, we assume that early (especially emotional) neglect in particular, but a disrupted early social environment in general, is common in BPD, and we assume that it can undermine the ability of some individuals to develop full mentalizing capacities. Second, we assume that, particularly in these individuals, subsequent adversity or trauma could further disrupt mentalizing, in part as an adaptive maneuver on the part of the child to limit exposure to a brutalizing psychosocial environment, and in part because of the high level of arousal generated by attachment hyperactivating and disorganized attachment strategies that serve to disrupt less well practiced and less robustly established higher cognitive capacities. Third, mentalizing is a multidimensional capacity, and thus different subtypes of BPD patients are characterized by specific impairments in these capacities.

Several predictions follow from these views. In BPD patients we expect to see higher levels of insecure attachment strategies and attachment disorganization in particular, an association with high levels of early (emotional) neglect and later trauma, and a complex pattern of sociocognitive (or mentalizing) deficits moderated by (1) the nature of the task; (2) the emotional and, in particular, the attachment demands the task places on the individual; and (3) the nature of the attachment history of the individual. We review evidence for each of these assumptions in the following sections.

Disordered Attachment in BPD

BPD and Attachment Disorganization

The mentalizing approach to BPD is strongly rooted within contemporary attachment theory. There are at least two strands of research supporting the link between BPD and attachment issues. The first strand has provided direct evidence for such a link by showing that BPD is associated with increased levels of insecure attachment styles, by using both interview-based assessments of attachment such as the Adult Attachment Interview (AAI), and self-report measures. The second strand relates to attachment trauma (Allen, 2013). These views are congruent with general biopsychosocial models of BPD (Oldham, 2009), assuming that adverse childhood experiences and genetic factors interact to create a unique combination of biological factors (neurobiological structures and dysfunctions) and psychosocial factors (personality traits, personality functioning) that underpin BPD pathology (affective and behavioral dysregulation and disturbed relatedness).

Within the empirically derived taxonomy of PD diagnoses, based on over 1,200 clinician ratings of the Shedler–Westen Assessment Procedure (SWAP-II, an assessment tool for personality classification), the borderline-dysregulated spectrum emerges as a coherent prototype characterized as fearful of rejection, abandonment, and isolation, and becoming attached quickly and intensely (Westen, Shedler, Bradley, & DeFife, 2012). We suggested some time ago (Fonagy & Higgitt, 1990; Fonagy, Target, & Gergely, 2000) that the hyperactivation of the attachment system may be a core aspect of BPD. In forming an attachment bond, children, when exposed to threat and experiencing fear and distress that activates the attachment system, are biologically predisposed to proximity seeking. Under optimal circumstances of caregiver sensitivity and responsiveness, a down-regulation of emotion and deactivation of the attachment system takes place, and a lasting bond is formed to the individual who was attentive to the child's need (Bowlby, 1969, 1973). However, where early relationships are disrupted, for reasons of biology, circumstance, or a combination of the two, the proximity seeking that is set in motion by the activation of attachment is expected to lead to further adverse emotional experience. This negative experience generates the emotional response of fear and distress that has evolved to trigger the attachment system, which then inevitably stimulates further proximity seeking in the increasingly forlorn hope of achieving down-regulation (Main, 2000). Within this model there is considerable room for individual differences to emerge; these differences are affected by genetic predisposition (Fearon, Shmueli-Goetz, Viding, Fonagy, & Plomin, 2013) and formative psychosocial experience (e.g., Fraley, Roisman, Booth-LaForce, Owen, & Holland, 2013; Repetti, Taylor, & Seeman, 2002).

There is a rich body of empirical data now available to support these speculations about the relationship between attachment and BPD. For example, one large investigation with over 1,400 participants compared competing multivariate models of adult attachment patterns, impulsivity, and trait negative affect as these related to borderline

features (Scott, Levy, & Pincus, 2009). The relationship between attachment anxiety and BPD features was most effectively modeled when seen as generating negative affectivity and impulsivity. This provided a better fit than the alternative model of impulsivity or negative affectivity generating attachment anxiety. The suggestion from this study is that impulsivity and negative affect can lead to BPD when these occur in the context of high levels of attachment anxiety.

Agrawal et al. (2004) reviewed 13 empirical studies of adult attachment styles of individuals with BPD, all showing an association between BPD and insecure attachment. These findings have been subsequently confirmed in comparisons with other PD groups (Aaronson, Bender, Skodol, & Gunderson, 2006; Barone et al., 2011; Fossati et al., 2005; Meyer, Ajchenbrenner, & Bowles, 2005; Scott, Kim, et al., 2013). Congruent with our assumptions, cross sectional investigations show those with borderline features to have preoccupied (reflecting attachment hyperactivating strategies), disorganized, and unresolved patterns of attachment (Levy, Beeney, & Temes, 2011). Yet, these studies are not particularly compelling because the symptomatology (and phenomenology) of BPD maps directly on to a pattern of preoccupied and disorganized attachment. If the desperate pursuit of comfort and reassurance is part of the definition of the disorder, it is hardly surprising that attachment patterns describing this behavior are found with greater frequency within this group. On the other hand, attachment formulations have undoubtedly influenced (diagnostic) descriptions of BPD and offer a presumed explanation of the psychological and neurobiological mechanisms underlying descriptive features of BPD. Nevertheless, we need to beware of allowing descriptions to masquerade as explanations. This imperative makes longitudinal developmental studies particularly valuable: unfortunately, only a handful of studies looking at early attachment and BPD as the outcome are available to date (Carlson, Egeland, & Sroufe, 2009; Lyons-Ruth, 2008), and most studies cover adolescent development only. For example, it has been found that adolescent behaviors that indicate impulsivity and deficits in self-regulation are predicted by a pattern of preoccupied attachment from age 13, through age 15, and up to age 17 (Kobak, Zajac, & Smith, 2009).

A further cross sectional study reported by Choi-Kain, Fitzmaurice, Zanarini, Laverdiere, and Gunderson (2009) was able to differentiate patients with mood disorder from those with BPD in terms of attachment style. While both MDD and BPD patients showed greater preoccupation and fearfulness than community controls (although BPD patients were more severely affected for both traits), only patients with BPD simultaneously showed preoccupation and fearfulness. This study confirms what a number of attachment theorists have suggested: that the key marker of BPD is a lack of any functional regulation strategy to reduce attachment distress (Fonagy & Bateman, 2008; Main, 2000).

Genetic Effects in BPD and Attachment

To use cross sectional data on the disorganization of attachment as an indirect indication of putative early environmental influences on BPD is further misguided in the light of evidence concerning the limited stability of attachment classification across development (e.g., Fraley, 2002) and emerging evidence on the genetic determinants of both attachment classification in adolescence and BPD. In our view, attachment theory, as conceived by John Bowlby, is a thoroughgoing biological model that is often mistakenly coupled to a naive environmentalist position. It would also be mistaken to assume that the mentalizing approach is yet another psychodynamic parent-blaming approach.

In fact, strong emerging evidence concerning the genetic determinants of BPD is fully consistent with an attachment theory perspective, and evidence is now overwhelming in relation to the genetic determination of BPD. Recent years have seen the publication of several reports confirming the familial nature of BPD (White, Gunderson, Zanarini, & Hudson, 2003; Zanarini, Barison, Frankenburg, Reich, & Hudson, 2009). Classical twin studies place heritability estimates of BPD at around 40–50% (Bornovalova, Hicks, Iacono, & McGue, 2009; Distel et al., 2008; Kendler et al., 2008; Torgersen et al., 2000). Adding siblings, spouses, and parents of twins to generate more complex behavioral–genetic models makes the genetic evidence even more persuasive (Torgersen et al., 2008). Molecular studies have, however, so far failed to identify a compelling anomaly associated with BPD (Leichsenring, Leibing, Kruse, New, & Leweke, 2011). Nor have molecular genetic studies of attachment been unequivocally successful. Several candidate gene studies have reported associations or gene–environment interactions in relation to attachment security in infancy, primarily involving polymorphisms in the dopamine D4 receptor gene, the serotonin transporter gene, and the oxytocin receptor gene (Barry, Kochanska, & Philibert, 2008; Chen, Barth, Johnson, Gotlib, & Johnson, 2011; Gervai et al., 2005; Gervai et al., 2007; Lakatos et al., 2000; Spangler, Johann, Ronai, & Zimmermann, 2009). None of these candidate gene associations has been consistently replicated, however, and the most recent paper on

the subject, which combined two relatively large cohorts, found no evidence of reliable single-gene associations or gene–environment interactions (Fraley et al., 2013; Luijk et al., 2011), although the stability of attachment security may have molecular genetic markers (Raby, Cicchetti, Carlson, Egeland, & Collins, 2013).

In contrast, behavioral–genetic studies of attachment are providing novel insights into the possibility of gene–environment interactions. Studies of early attachment have consistently yielded negative results in regard to the heritability of attachment classifications in infancy and toddlerhood. Where behavioral–genetic studies have found evidence of shared environmental effects on development in other domains, they have tended to involve younger samples (infants and preschoolers); this suggests that shared environmental effects may be relatively restricted to infancy and toddlerhood and may not always be stable beyond these early years (Plomin, DeFries, Knopik, & Neiderhiser, 2013). A recent study of attachment in adolescence has shown a powerful genetic component (Fearon et al., 2013). This is consistent with the common observation that genetic influences on a number of psychosocial traits begin to show their effects at later developmental phases. It is possible that the child's genes could come to influence attachment only in later development because they increasingly influence parental attitudes and caregiving behavior (gene–environment correlation; see Price & Jaffee, 2008). Particularly in relation to attachment, it seems that we may assume that there is considerable selective advantage in interpersonal styles being exclusively responsive to caregiver behavioral characteristics at the age of greatest parental dependence. Into adolescence, attachment styles may then become increasingly influenced by genetic predisposition as the individual has greater opportunities to impose his or her genetic makeup on the quality of an emerging attachment relationship.

However, to discount entirely the significance of early attachment experiences in the emergence of BPD on the basis of genetic data would fly in the face of other substantial and rapidly accumulating evidence. Genetic studies are also seriously hampered by methodological issues in the assessment of attachment across the life span (Roisman et al., 2007). Further, the powerful association between social inequality and the prevalence of health and social problems makes an incontrovertible case for the role of social determinants in developmental psychopathology. Wilkinson and Pickett (2009), for example, provided ample evidence that countries with the highest levels of income inequality also manifest higher levels of the kind of mental health and social problems we normally associate with the borderline syndrome (e.g., drug and alcohol addiction, teenage births). In fact, on the basis of studies that use interview-based estimates of population prevalence of BPD, we can make a reasonable prediction of BPD prevalence from the ratio of the average income of the richest 20% to that of the poorest 20% of the population. We make this point not simply to underscore the importance of social determination, but also to sound a note of caution. Across roughly the first three-quarters of the twentieth century, the unequal distribution of income in terms of the proportion of wealth held by the top 1% of the society generally decreased in most Western countries (from over 20% to under 10%), having reached a historic peak of inequality in the late nineteenth century. However, the United States experienced a dramatic reversal of this trend in the 1980s and the first decade of this century, and the figure now hovers at between 20 and 25%. A similar pattern is evident in the United Kingdom, although the figure remains under 20%. Even more traditionally egalitarian countries, such as Sweden, appear to be following suit. If the relationship between a lack of apparent social concern and BPD prevalence is causal, we may well anticipate a dramatic increase in prevalence; this may indeed be already indicated by some figures (Grant et al., 2008).

Gene–Environment Interactions

Increasingly, authors have therefore been considering interactional models, which incorporate biological vulnerability with psychosocial risks such as early neglect and abuse, and pinning their hopes on emergent studies of gene–environment interactions (e.g., Wagner, Baskaya, Dahmen, Lieb, & Tadic, 2010; Wagner, Baskaya, Lieb, Dahmen, & Tadic, 2009). Modern psychodynamic views could usefully revisit classical psychoanalysis (e.g., Freud, 1896/1962, 1905/1953; Freud & Breuer, 1893/1962), which saw genetic factors in combination with adverse childhood experiences as the cause of both biological (neurobiological structures and dysfunctions) and psychosocial (neuroticism, interpersonal and self-structure deficits) anomalies. Joel Paris (2011), among others, has identified the urgent need to consider biological and environmental factors together in studies of the emergence of PD.

As noted, a BPD gene has not been identified so far, but researchers are perhaps gradually approaching the identification of an endophenotype for the disorder. For example, impulsive aggression and suicidal behavior have been linked to the tryptophan hydroxylase (TPH) gene, and patients with BPD have a higher frequency of two of eight polymorphisms in one of the two known isoforms of the TPH gene (Ni, Chan, Chan, McMain, & Kennedy, 2009).

Impulsive aggression is also associated with reduced serotonergic responsiveness and the inefficient (short or s) allele of 5-HTTLPR, which has been more commonly identified in patients with BPD (Ni et al., 2006) in some but not all reports (e.g., Pascual et al., 2008). There are interesting suggestions that the s allele marks a vulnerability to stressful life events (Caspi et al., 2003) on the one hand, and the positive influence of maternal sensitivity on the other (Barry et al., 2008). Accumulating evidence supports the view that the s allele, in combination with secure attachment, increases agreeable yet autonomous social behavior in adolescents (Zimmermann, Mohr, & Spangler, 2009). The same polymorphism in combination with insecure parenting predicts poor self-regulation (Kochanska, Philibert, & Barry, 2009) and impulsiveness in response to threats to autonomy (Zimmermann et al., 2009). The challenging suggestion is that the inefficient s allele may be retained in the gene pool because in favorable circumstances it enhances social sensitivity, potentially making a child both more and less prosocial depending on the emotional environment.[3]

There may be further epigenetic evidence of the complexity of gene–environment interactions. A recent study hinted at the role of environmental influence in the penetration of the 5-HTTLPR polymorphism. It seems that, in line with the environmental vulnerability of those with the s allele, attachment disorganization (indicated by unresolved loss and trauma scores) is elevated for those with the s allele only in cases with lower levels of methylation (van IJzendoorn, Caspers, Bakermans-Kranenburg, Beach, & Philibert, 2010). This literature promises to yield further exciting developments, and there may indeed be genetically determined serotonergic anomalies that underpin the kind of aggressive impulsive symptoms that Kernberg (1967) placed at the center of his psychoanalytic theoretical model. The molecular nature of this association remains unclear at this time, but the adequate consideration of triggering psychosocial relational environment factors seems key to a proper understanding of the biological narrative (Wagner et al., 2010).

The role of environmental factors appears to be cumulative. In a twin study of over 5,000 twins and almost 1,300 siblings, Distel et al. (2011) showed that the unique environmental variance identified by the behavioral–genetic model increases linearly with the number of traumatic life events to which an individual is exposed (from 54% with no events to 64% with six events), while neither additive genetic variance nor dominant genetic variance changes. The proportion of variance accounted for by the genetic contribution declines linearly with exposure to social adversity, and decreases from 46% to 36% when those exposed to no traumatic life events are contrasted with those who report six or more of such events (Distel et al., 2010).

Biological vulnerability to environmental events was also illustrated by Belsky et al. (2012). A family history of psychopathology was studied in a nationally representative birth cohort of over 1,100 families with twins. When the children were 12 years old they were assessed using a self-report measure of BPD. In the presence of a family history of psychopathology, 47% of those in whom maltreatment was observed were in the extreme group (they topped the 95th percentile). By contrast, maltreatment in the absence of a family history of psychopathology was found in only 7% of the subjects in the BPD category. The same indication of a diathesis–stress interaction was found for maternal negativity and a dimensional measure of BPD. Maltreatment was only weakly associated with BPD symptoms overall. When genetic vulnerability (operationalized as *any* family history of psychological illness) was used as a moderator, maltreatment became a highly significant predictor of membership of the BPD group. The relative risk of BPD was only about twofold for those with an experience of maltreatment who carried no genetic risk via a family history of mental disorder. However, among those with a family history of psychiatric illness (taken to indicate a genetic vulnerability), experience of early maltreatment increased the risk of membership of the BPD group by a factor of 13. Further, maternal negative expressed emotion about the child, recorded when the child was 5 years of age, was twice as strongly associated with borderline personality characteristics among those with genetic vulnerability/family history as among those without.

This limited set of observations could be seen as confirming the evolutionary-neurodevelopmental theory on differential susceptibility to the environment (Belsky & Fearon, 2008; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011), which suggests that children vary in how they respond to the psychosocial environmental context. Some (low-susceptibility) children are expected to do similarly well irrespective of the environmental context. Other children are assumed to have a genetically

[3]It may be interesting to note that collectivistic nations (e.g., Korea and China) that particularly value interdependence appear to have a higher prevalence of s allele carriers and social susceptibility genes more generally than nations where individualism is more highly valued (Chiao & Blizinsky, 2010), providing evidence for so-called gene–culture coevolution (Luyten & Blatt, 2013).

transmitted susceptibility to environmental influence and are consequently more susceptible to abusive childhoods. For this phenotype to remain in the gene pool we must assume that (1) these children benefit more from favorable circumstances and (2) they find ways to adapt to malevolence and adversity and respond to threat by reducing the experience of pain, even if, compared with less susceptible individuals, they appear to be engaging in behaviors that are maladaptive (e.g., self-harming, risk-taking).

Two separate UK longitudinal cohort studies bring together risk factors of maltreatment, bullying, and BPD (Shakoor et al., 2012; Wolke, Winsper, & Hall, 2012). The E-Risk study, an environmental risk longitudinal twin study of over 2,200 children and families, demonstrated lower mentalizing capacities, as assessed with a theory of mind (ToM) task, in individuals who showed clear indications of emergent BPD in early adolescence (Belsky et al., 2012). ToM performance also predicted more general interpersonal difficulties, particularly becoming a victim, being a bully, or, most unequivocally, being a bully–victim (i.e., a bully who has a history of being a victim) (Shakoor et al., 2012). A longitudinal study on a separate sample, the Avon Longitudinal Study of Parents and Children, found that the risk of BPD symptoms increased with increased risk of bully–victimization (Wolke, Winsper, et al., 2012). Both these findings underscore that, as well as focusing on parent–child relationships, the nature of peer relationships as mediating factors should be included in biopsychosocial models of BPD, in the light of the anomalous capacity for social cognition (Sansone, Lam, & Wiederman, 2010; Wolke, Schreier, Zanarini, & Winsper, 2012). The extent to which this pathway may run parallel to or may be independent from maltreatment in mid-childhood is unclear. In the E-risk study, ToM deficit predicted bully–victim status when maltreatment was controlled for. In the Avon study, bully–victimization rather than maladaptive parenting mediated the relationship between childhood dysregulation and BPD symptoms. It is possible that bully–victimization leads to an exacerbation of dysfunctional social cognition such as hypermentalization. A likely explanation may be that some of the key etiological effects of parenting, perhaps with the exception of the most severe forms of persistent brutalizing of children, are primarily felt in early childhood (Winsper, Zanarini, & Wolke, 2012) through initiating a cascade of events (Bornstein et al., 2006).

When it comes to the transgenerational transmission of BPD, a significant aspect of the gene–environment model is the parent–child interaction in families where mothers have a diagnosis of BPD. Negative parent–child relationships are more likely where children manifest high emotional reactivity, and such relationships are likely, in turn, to exacerbate internalizing and externalizing symptoms (Feinberg, Button, Neiderhiser, Reiss, & Hetherington, 2007). By contrast, there is indirect evidence that warm, accepting parenting can moderate some of the outcomes of genetic and physiological vulnerabilities (Eley et al., 2004). There is also evidence that points to genetic factors protecting from even adverse social environments (e.g., Kaufman et al., 2006).

There are preliminary data from a number of small-sample studies (Crandell, Patrick, & Hobson, 2003; Hobson, Patrick, Crandell, Garcia-Perez, & Lee, 2005; Newman, Stevenson, Bergman, & Boyce, 2007) that maternal BPD can impact on infant affect as well as capacities for self-regulation. Hobson et al. (2005) reported high levels of infant attachment disorganization in 12-month-old infants of mothers with BPD. Stepp, Whalen, Pilkonis, Hipwell, and Levine (2012) have summarized the literature on parenting behaviors of mothers with BPD, highlighting insensitive forms of communication (including frightening statements and actions, intrusion, and unwarranted criticism), role confusion, and high levels of reported distress. The literature, however, is not consistent. In a relatively large-scale investigation of 200 mothers, Conroy, Marks, Schacht, Davies, and Moran (2010) found no effect of Cluster B PD status on maternal involvement and maternal sensitivity. The interactions were short, however, and 2 months following childbirth may not be an ideal time for identifying pathological outcomes.

Implications for a Developmental Understanding of BPD

The main implications of a bidirectional model of environmental (including attachment issues) and genetic/biological factors in BPD are far-reaching, although such a bidirectional model is by no means new in accounts of BPD (Crowell et al., 2005; Fonagy, 1998; Gunderson & Lyons-Ruth, 2008; Paris, 2005; Zanarini & Frankenburg, 2007). From a mentalizing perspective, it is inconceivable that a proper understanding of borderline pathology can be arrived at without thought being given to the nature of early object relationships. For a start, an immediate implication of a genetic model of BPD is that the parents of these individuals would be likely to manifest BPD traits or even frank BPD, which would profoundly impact on their caregiving. The implication therefore goes beyond mere gene–environment correlations (Plomin & McGuffin, 2003) and suggests quite specific developmental paths for social inheritance. For example, children of mothers with BPD show deficits in emotion regulation and distorted self–other representations, as well as later problems in

psychosocial functioning (Hobson et al., 2005; Hobson et al., 2009).

Given the difficulties these patients have in affective communication and relatedness in their moment-to-moment interactions with others, it would be surprising if their children were spared the impact of these shortcomings, which directly interfere with the caregiving function (Bowlby, 1988; Sroufe et al., 2005). Young children of mothers with BPD often manifest disorganized attachment (Hobson et al., 2005), which is associated with disrupted affective communication and fearful and disoriented responses from the mother (Hobson et al., 2009). A fearful pattern of attachment persists in these children until adolescence; they show an inability to make close friends or to feel socially accepted (Herr, Hammen, & Brennan, 2008). In mid-childhood, the children of mothers with BPD show increased fear of abandonment, fantasy-proneness and role reversal when completing story stems (Macfie & Swan, 2009). Macfie (2009) reported that a girl aged 5, whose mother had BPD, completed a story about a birthday party using family dolls, a table, and a cake thus: "The girl tells how the family open presents and eat cake. She then adds: *And then Mom takes off her clothes and gets drunk*" (p. 69).

The social environment of infancy thus can still be thought of as critical because the infant acquires a sense of self through interactions with the object (Fairbairn, 1952a, 1952b). Early attachment experiences therefore should be robust predictors of BPD pathology in later life, not so much because of the attachment experiences themselves, but because it is in the context of these attachment relationships that the infant comes to understand his or her own emotional states, acquires the capacity for affect regulation, and discovers him/herself as a psychological entity through marked mirroring interactions (Fonagy, Gergely, Jurist, & Target, 2002; Fonagy, Gergely, & Target, 2007a).

The evidence linking harsh treatment in early life with later BPD goes beyond patient recollections; it has been largely confirmed by numerous prospective studies (Carlson et al., 2009; Crawford, Cohen, Chen, Anglin, & Ehrensaft, 2009; Johnson, Cohen, Chen, Kasen, & Brook, 2006). Microanalytic studies of parent–infant interaction have contributed to our understanding of the way the child's genetic predisposition may compound the effects of suboptimal parenting environment to increase the risk of attachment disorganization (Beebe et al., 2010) and BPD symptoms (Lyons-Ruth & Jacobvitz, 2008). In Lyons-Ruth's longitudinal study (Lyons-Ruth, 2008), disrupted maternal communication and maltreatment were found to be independent predictors of BPD symptoms at age 18. An unusual longitudinal study by Crawford et al. (2009) examined the trajectory of BPD symptoms over time, and found deprivation of early parenting influence (early separation) to be predictive of BPD symptoms in adolescence and early adulthood, and a slower developmental decline of symptom severity over this period. Importantly, temperament (presumably genetically determined) was a partial mediator between early development and later BPD symptoms. We can speculate that individuals with a difficult temperament are, on the whole, somewhat more likely to be abandoned by parents who are themselves more impulsive and less able to feel emotional commitment toward the child (gene–environment correlation, as described earlier in this chapter). It is also likely that this type of environmental deprivation will cause these individuals to miss out on the self-organizing influence of early parenting; they will additionally be more likely to experience negative parenting events in a more exaggerated manner, turning on themselves in relation to deprivation, blaming themselves for the separation, and ending up feeling unworthy of love and attention.

The same bidirectional process is brought into relief by a carefully conducted longitudinal study of the emergence of borderline symptoms in young adulthood. Carlson and colleagues (2009) reported significant, but weak, correlations between borderline symptoms at 28 years of age and indicators of a suboptimal early environment (maltreatment, maternal hostility, attachment disorganization, and family stress in the first 3–4 years of life). These culminated in a range of social-cognitive anomalies—attentional disturbance, emotional instability, and relational disturbance—that were evident by 12 years of age. A path-analytic approach offered strong evidence that disturbances in self-representation in early adolescence mediated the link between disorganization of early attachment relationships and PD. A narrative projective task administered at age 12 yielded more intrusive violence related to the self, more unresolved feelings of guilt and fear, and more self-associated bizarre imagery in individuals who showed borderline symptoms 16 years later. Early adversity was strongly associated with these anomalies. A combined indicator of early adversity predicted such effects both directly and indirectly via the disorganization of the attachment system. Anticipating our discussion of findings concerning impairments in mentalizing in BPD discussed later in this chapter, Carlson and colleagues conclude that "representations and related mentalizing processes are viewed as carriers of experience that link early attachment to later psychopathology" (p. 1,328).

BPD and Childhood Adversity

The role of developmental trauma in BPD in general has been a significant focus of research and further amplifies our considerations concerning the importance of attachment disruptions in relation to BPD.

Among individuals with PDs, rates of childhood trauma are high (73% report abuse, of which 34% is sexual abuse, and 82% report neglect; Ball & Links, 2009). Compared with nonclinical adults, PD patients are four times as likely to have suffered early trauma (Johnson, Cohen, Brown, Smailes, & Bernstein, 1999). Childhood physical abuse increases the risk for adult antisocial, borderline, dependent, depressive, passive-aggressive, and schizoid PDs (McGauley et al., 2011). BPD is more consistently associated with childhood maltreatment than are other PD diagnoses (Baird, Veague, & Rabbitt, 2005; Battle et al., 2004; Buchheim et al., 2008; Fonagy & Bateman, 2008; Fonagy, Target, Gergely, Allen, & Bateman, 2003; Johnson et al., 1999; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002).

A particularly impressive study following up several hundred abused and neglected children and matched controls into adulthood reported a 2.5-fold increase in the prevalence of BPD associated with abuse and neglect (Widom, Czaja, & Paris, 2009). In this prospective investigation of children who were identified as maltreated by child protection services, early neglect appeared to be the most potent risk factor for both genders, whereas physical abuse represented a risk only for males. Of course, not all those with a history of abuse go on to develop BPD; Widom et al. (2009) found that only 14.9% of those who had been abused met criteria for BPD. Conversely, there is a substantial proportion of individuals with confirmed BPD who do not report abuse in childhood, with rates varying between 8% (Kingdon et al., 2010) and 70% (Afifi et al., 2011) depending on the population sampled. Sexual abuse, which has been highlighted by retrospective studies as a potentially causative factor in BPD, appeared not to increase the risk of BPD for either gender. In general, findings highlight the pernicious impact of early neglect. In our opinion, this is important to underline, as early neglect critically deprives children of the opportunity to use interpersonal interactions with the caregiver to acquire knowledge and control over their subjective worlds—that is, to acquire the capacity for mentalizing.

In our view, at the present state of knowledge, the existence of an association between adversity and BPD is less in question than the nature of the potential mediating variables linking maltreatment (and neglect in particular) to BPD. In what is perhaps the most thoughtful review of this literature so far, Ball and Links (2009) attempted to use Hill's epidemiologic criteria for *causality* (relationship strength, temporality, dose response, specificity, consistency, epidemiologic and biologic plausibility, and analogy) to determine the status of the association between childhood trauma and BPD. As Ball and Links note, several systematic reviews offer strong evidence for an association between child abuse and psychosis (e.g., Read & Bentall, 2012), bipolar disorder (e.g., Daruy-Filho, Brietzke, Lafer, & Grassi-Oliveira, 2011), and depression (e.g., Nanni, Uher, & Danese, 2012). Despite lack of evidence for specificity (i.e., some individuals experience BPD in the absence of trauma, while many experience trauma without developing BPD), Ball and Links (2009) nevertheless conclude that a causal relationship between trauma and BPD is likely. In their review of pathways to BPD, Chanen and Kaess (2012) similarly conclude that studies of both clinically and nationally representative samples confirm that a range of cumulative aversive events contributes to the development of BPD.

However, frank abuse cited by BPD patients occurs mostly in adolescence (e.g., Pietrek, Elbert, Weierstall, Muller, & Rockstroh, 2013). In drawing up a mentalizing, developmental model of BPD in relation to childhood adversity, we suggest that two processes unfold, which have a cumulative effect. First, we assume that the development of mentalizing depends on the social co-construction of internal states between child and parents. Following on from this, we hypothesize that early neglect and an early emotional environment incompatible with the normal acquisition of understanding oneself and others creates vulnerability for BPD. Second, we further hypothesize that subsequent brutality in an attachment context can disrupt mentalization as part of an adaptive adjustment to adversity when a child—whose early experiences of neglect have left them less resilient to deal with trauma—is in a state of helplessness in relation to those individuals (Fonagy, Steele, Steele, Higgitt, & Target, 1994; Stein, Fonagy, Ferguson, & Wisman, 2000). In summary, we propose (Fonagy & Luyten, 2009) that early emotional neglect in particular, rather than physical or sexual abuse as such, predisposes an individual to developing BPD by limiting his or her opportunity to acquire mentalization and leaving the capacity to mentalize vulnerable to disruption under the influence of later stress.

We further assume (and will review evidence related to this below) that childhood environments that are

emotionally abusive, or in which the discussion and validation of mental states are absent, lead to the generation of coping strategies that favor rapid intuitive (as opposed to more deliberative reflective), emotion-focused (as opposed to cognition-focused) mentalizing—particularly in individuals primed to rapidly identify risk by an experience of early neglect. This intuitive state is dominated by mental-state attributions based on external observable cues (as opposed to the inference of internal states, which may be unreliable in a maltreating environment). In addition, such individuals may need to develop a strategy of being highly sensitive to and readily influenced by (mirroring) mental states in others (at the cost of achieving a clear differentiation of self and others' mental states; Fonagy, 2000; Fonagy & Luyten, 2009; Luyten, Fonagy, Lowyck, & Vermote, 2012). We wish to emphasize that while this approach may appear to suggest a deficit theory, our emphasis is upon adaptation. The specific configuration of mentalizing capacities characterizing individuals with BPD may be conceived of as that most likely to favor survival under conditions of significant adversity (Frankenhuis, Panchanathan, & Clark Barrett, 2013). Our model is fully compatible with Linehan's (1993) original biosocial theory of the development of BPD and its later elaboration (Crowell et al., 2009), which highlights that an invalidating childhood environment can serve to undermine the understanding, regulation, and toleration of affect states, leading the child to adapt by displaying more extreme emotions to achieve a contingent response from carers (the so-called intermittent reinforcement of extreme emotional outbursts).

There is indeed some evidence to support these assumptions, although most reviews of childhood trauma in BPD (Ball & Links, 2009; Chanen & Kaess, 2012) combine reviews of abuse with neglect. Yet, in view of the specific predictions we make in relation to neglect, a separate consideration of the neglect and emotional abuse literature is appropriate here. In contrast to the relatively incontestable ways physical and sexual abuse can be objectively defined, neglect and emotional maltreatment are harder to pinpoint (Kempke et al., 2013). Glaser (2002) defines emotional abuse and neglect as (1) being emotionally unavailable or unresponsive to the child, (2) placing negative attributions and misattributions upon the child, (3) engaging in developmentally inappropriate or inconsistent interactions with the child, (4) failing to recognize the child's boundaries and individuality, for example, using the child for the fulfillment of the parent's own psychological needs, and (5) failing to promote the child's social adaptation.

In a systematic literature review, Crombie and Fonagy (2015) identified 298 studies relevant to BPD and trauma that were reported between 1980 and 2012. Of these, 202 could be excluded because they failed to measure BPD or trauma systematically. Of the 99 remaining studies (three were added following hand searching), 60 were excluded because they measured only physical or sexual abuse, did not involve a clinical population, or had no systematic measure of childhood trauma. The final 39 studies reported on 33 independent samples, mostly using the Structured Clinical Interview for *DSM-IV-TR* Axis II Personality Disorders (SCID-II) as a diagnostic instrument and a combination of self-report and interview-based measures of trauma. There were eight cohort, 18 cross sectional, and 13 case–control studies, each with specific methodological limitations. Cross sectional studies invariably raise questions concerning the validity of the retrospectively measured trauma, which may be undermined and confounded by concurrent symptomatology (Widom et al., 2009). Indeed, there are a range of methodological concerns specific to BPD that may make one suspect the veracity of BPD patients' reports of childhood experience, including misinterpretation, exaggeration, or even fabrication of caregiver behavior (Zanarini et al., 2000), negative bias toward traumatic events and parental failings (Huang et al., 2012; Machizawa-Summers, 2007), and reporting maltreatment as a means of actively seeking sympathy (Battle et al., 2004). However, such designs can be of great use in estimating the prevalence of disorders and causal factors (Mann, 2003). There is also indirect support for the validity of retrospective data from studies where family members were asked to verify patients' self-reports of trauma histories (Laporte & Guttman, 2001; Laporte, Paris, Guttman, & Russell, 2011).

Prospective cohort studies overcome reporting bias, but have their own weaknesses. By definition, their sampling frame will be arbitrary or driven by the theoretical considerations dominant at the time of study design. They are likely to capture only a selection of those who will develop BPD, raising questions not only of statistical power, but also of the representativeness of the sample (Cohen, Crawford, Johnson, & Kasen, 2005). More pertinent in the context of neglect is the inevitable limitation of prospective studies to use time-bound (historical) definitions of risk. Awareness of emotional neglect and abuse, as defined by Glaser (2002), is relatively recent and may have been missed in many earlier investigations (Cawson, Wattam, Brooker, & Kelly, 2000). Eleven studies (Driessen et al., 2000; Giesen-Bloo & Arntz, 2005; Horesh, Ratner,

Laor, & Toren, 2008; Lange, Kracht, Herholz, Sachsse, & Irle, 2005; Laporte & Guttman, 2001; Laporte et al., 2011; Lobbestael & Arntz, 2010; Lobbestael, Arntz, & Sieswerda, 2005; Sieswerda, Arntz, Mertens, & Vertommen, 2007; Weniger, Lange, Sachsse, & Irle, 2009; Wingenfeld et al., 2011) comparing emotional abuse and neglect in healthy controls and BPD patients reported higher levels in the patient groups, with two studies (Lange et al., 2005; Weniger et al., 2009) reporting a specific effect for neglect. Fourteen studies identified in the review compared neglect and emotional abuse in groups of patients with Axis I disorders and BPD (Battle et al., 2004; Bellino et al., 2005; Bornovalova, Levy, Gratz, & Lejuez, 2010; Giesen-Bloo & Arntz, 2005; Gratz, Tull, Baruch, Bornovalova, & Lejuez, 2008; Horesh et al., 2008; Huang et al., 2012; Joyce et al., 2003, 2006; Kingdon et al., 2010; Laporte & Guttman, 2001; Machizawa-Summers, 2007; Sieswerda et al., 2007; Wingenfeld et al., 2011). Two studies focusing on emotional neglect and abuse (Machizawa-Summers, 2007; Sieswerda et al., 2007) reported large odds ratios compared with non-PD Axis I disorders. Huang et al. (2012) found that the differences were significant for both mothers and fathers, and four of the six studies making specific comparisons with MDD found BPD groups to have experienced significantly higher levels of abuse and neglect (Battle et al., 2004; Bellino et al., 2005; Joyce et al., 2003, 2006). Only two studies (Horesh et al., 2008; Wingenfeld et al., 2011) reported no difference. These studies suggest that patients with BPD may experience more neglect or abuse than control patients with Axis I disorders.

Crombie and Fonagy also discuss 11 studies (Battle et al., 2004; Giesen-Bloo & Arntz, 2005; Goodman et al., 2003; Huang et al., 2012; Joyce et al., 2003, 2006; Lobbestael & Arntz, 2010; Lobbestael et al., 2005; Sieswerda et al., 2007; Zanarini et al., 2000; Zhang, Chow, Wang, Dai, & Xiao, 2012) that compared neglect and emotional abuse among groups with Axis II diagnoses. The large majority of these studies found BPD diagnosis to be specifically linked to emotional neglect or abuse. In a study reported by Zhang et al. (2012), emotional neglect was found to be a significant predictor of any PD diagnosis. However, rates of emotional neglect appear similar for antisocial PD and BPD (Battle et al., 2004; Lobbestael & Arntz, 2010; Lobbestael et al., 2005). Taking these studies together, it seems reasonable to conclude that individuals with BPD are more likely to report experiencing emotional neglect and abuse than those with most other PDs.

Further evidence of this association comes from studies correlating BPD symptoms or traits with self-rated emotional abuse and neglect (Afifi et al., 2011; Bierer et al., 2003; Bradley, Jenei, & Westen, 2005; Gratz, Latzman, Tull, Reynolds, & Lejuez, 2011; Specht, Chapman, & Cellucci, 2009). Of course, emotional abuse may be predictive of other types of PD (e.g., Afifi et al., 2011), but for BPD the association can be found at an early age (Gratz et al., 2011; Joyce et al., 2003, 2006; Zanarini, Frankenburg, Hennen, Reich, & Silk, 2006). Tyrka, Wyche, Kelly, Price, and Carpenter (2009) contrasted abused and nonabused PD patients and found higher levels of BPD among those with histories of emotional neglect and abuse.

Importantly, results obtained from longitudinal cohort studies confirm that emotional neglect and abuse predict the emergence of BPD symptoms in later life. In a follow-up of adults who were inpatients in adolescence, Helgelend and Torgerson (2004) reported that instability and emotional abuse were higher among those later presenting with BPD. Several publications from the Children in the Community (CIC) study (Johnson et al., 2001; Johnson, Smailes, Cohen, Brown, & Bernstein, 2000) have reported that supervision neglect combined with verbal abuse is a significant predictor of BPD symptoms. In a more recent report on the same cohort, Crawford et al. (2009) reported that those experiencing early separation have a slower rate of decline of BPD symptoms from adolescence. In one of the best-controlled studies to date, Widom et al. (2009) reported BPD to be significantly more likely to be present in adults who had legal records of childhood emotional neglect. Finally, in a small-scale study, Carlson et al. (2009) found a combination of early maltreatment, attachment disorganization, and general disturbance of the parent–child relationship to be a significant predictor of BPD symptoms in adulthood.

It is difficult to disentangle the impact of neglect and emotional abuse from that of physical or sexual abuse, as these types of early adversity often co-occur. For instance, 13 of the studies identified in Crombie and Fonagy's (2015) review also reported elevated levels of physical and sexual maltreatment. This is not surprising, given that sexual and physical abuse are more likely to occur in households characterized by emotional neglect. However, the particular heft of neglect and emotional abuse in the BPD profile is underscored in the studies that failed to find a significant difference in BPD prevalence in relation to sexual abuse (Bellino et al., 2005; Bierer et al., 2003; Laporte et al., 2011; Widom et al., 2009; Zanarini et al., 2000) or physical abuse (Battle et al., 2004; Widom et al., 2009 [in male patients only]; Wingenfeld et al., 2011), yet yielded significantly higher BPD prevalence in association with emotional neglect and abuse. In three studies (Gratz et al., 2008; Machizawa-Summers, 2007; Zhang et al., 2012),

emotional neglect and abuse were significant predictors of BPD symptoms over and above all other types of abuse. In the study of Specht et al. (2009), lack of emotional support was shown to be the only significant predictor of BPD symptoms.

In conclusion, generally high-quality studies across a range of designs and measurement methodologies converge in showing, both prospectively and retrospectively, that emotional neglect and abuse predict BPD symptoms and diagnosis in line with or in excess of the impact that can be observed to be associated with physical and sexual abuse. The risk associated with emotional neglect and abuse is at least comparable with that of physical and sexual maltreatment (see, e.g., Tyrka et al., 2009). In line with our views, we feel this observation to be critically important because we expect that even in the absence of dramatic maltreatment, the individual's competence to represent mental states may be undermined by the absence of contingent responding to their subjective experience, resulting in increased vulnerability for BPD.

Disruptions of the Caregiving Environment and the Development of Mentalizing

Many studies support the suggestion that secure children are better than insecure children at mentalization tasks (see, e.g., de Rosnay & Harris, 2002). The first of these findings, reported from the London Parent–Child Project (Fonagy, Steele, Steele, & Holder, 1997), found that 82% of children who were secure with their mother in the Strange Situation test passed Harris's Belief-Desire Reasoning Task at 5.5 years, compared with 50% of those who were avoidant and 33% of the small number who were preoccupied. As we will show in more detail below, findings along these lines are not always consistent (see, e.g., Meins et al., 2002), but it generally seems that secure attachment and mentalization are subject to similar social influences.

Before reviewing the relevant research, it is, first of all, necessary to identify what it is about emotional abuse and neglect that may leave the child with this increased vulnerability to BPD. We (Fonagy & Luyten, 2009) have stressed the importance of secure attachment in providing a context in which the child is allowed to develop the ability to mentalize and regulate his or her own emotions. Clearly, in an environment that is invalidating and emotionally abusive, an insecure and disorganized attachment pattern is likely to develop (Fonagy, 2000; Fonagy & Luyten, 2009). We contend that it is the absence of this safe base from which to learn the capacity to mentalize and self-regulate that can create a greater vulnerability for developing BPD later in life. In this section we examine the relationship between the emotional environment, the obstruction of acquisition of general mentalizing abilities, and the emergence of BPD. More specific mentalizing impairments in relation to BPD will be discussed further on.

Emotional dysregulation (Gratz et al., 2008), schema modes (particularly disconnection/rejection and impaired limits) (Specht et al., 2009), and distorted self-representation in middle childhood (Carlson et al., 2009) have all been shown to mediate the relationship between childhood abuse and BPD. However, these studies used a composite score of maltreatment rather than looking more specifically at particular aspects of emotional abuse and/or neglect. Rogosch and Cicchetti (2005) found that attentional networks and processes did not mediate the precursors to BPD in abused children. The formation of schemas and the representation of the self, often conspicuously impoverished in individuals with BPD, are themselves mediated by selective disruption of social cognition (Carlson et al., 2009). These studies point to the importance of these key psychological processes in mediating the impact that the experience of trauma in childhood has on the development of BPD symptoms in later life. More work is needed in this area, but the available research suggests that the key psychological processes that make the impact of trauma on personality development so harmful and enduring relate to the emergence of the concept of self and identity.

Significantly, Widom et al. (2009) found that the impact of child abuse and neglect (all types) became nonsignificant in a regression model when other family and lifestyle characteristics were included (e.g., parental substance use, employment, education level, and Axis I disorders); these authors concluded that maltreatment may represent a marker for family dysfunction, and that it is this family dysfunction that may actually be more significant in leading to a greater risk of BPD. This is also congruent with the notion that abuse and neglect are typically part of a broader context characteristic of risky families and environments (Repetti et al., 2002) or pathogenic relational environments (Cicchetti & Toth, 2005). A number of family-related factors—all likely to undermine the acquisition of mentalizing—were reported to be significant predictors of BPD: these included parental psychopathology (Afifi et al., 2011; Helgeland & Torgersen, 2004; Widom et al., 2009; Zanarini et al., 2006), witnessing domestic violence in childhood (Afifi et al., 2011; Zanarini et al., 2006), and parental imprisonment and suicide attempts (Afifi et al., 2011). As noted, early neglect seems to be particularly pernicious in predicting strong associations with BPD symptoms in both men and women (Carlson et al., 2009; Crawford et al., 2009; Johnson, Cohen, Chen,

et al., 2006; Johnson, McGue, & Iacono, 2009; Widom et al., 2009).

However, more detailed prospective studies of caregiver–child interactions are needed to further investigate these assumptions. Existing studies in this context (Carlson et al., 2009; Lyons-Ruth, 2008) do suggest that parenting behavior is implicated in the development of BPD, but also show that anomalous development is often predicted by quite subtle anomalies of caregiver–child interaction. Yet, the demanding coding methods used in these studies create challenges for replication, particularly for population-representative studies. With increasing interest in the diagnosis, a number of ongoing and planned birth cohort studies and other longitudinal studies include BPD as an outcome. The measures of environmental influence in these studies often remain fairly broad, however, and able to detect only the crudest indicators of suboptimal childhood experience. Nevertheless, growing up in an environment of insecure and unpredictable attachment relationships may be expected to disrupt the acquisition of robust mentalization.

Maltreatment thus not only disorganizes the attachment system (see Cyr, Euser, Bakermans-Kranenburg, & Van IJzendoorn, 2010 for a comprehensive review), there is also evidence to suggest that it may disrupt mentalization. An accumulating body of evidence indicates that childhood maltreatment can have a negative impact on several aspects of social-cognitive competencies in individuals who are not yet explicitly diagnosed with a mental disorder (Cicchetti, Rogosch, Maughan, Toth, & Bruce, 2003; Pears & Fisher, 2005; Smith & Walden, 1999). Young maltreated children display impairments with regard to several indices of mentalizing: (1) they engage in less symbolic and less child-initiated dyadic play (Alessandri, 1991; Valentino, Cicchetti, Toth, & Rogosch, 2011); (2) they sometimes fail to show empathy when witnessing distress in other children (Klimes-Dougan & Kistner, 1990); (3) they have poor affect regulation, which contributes to later psychopathology and peer rejection (Kim & Cicchetti, 2010; Maughan & Cicchetti, 2002; Robinson et al., 2009); importantly, (4) they make fewer references to their internal states (Shipman & Zeman, 1999); and (5) they struggle to understand emotional expressions, particularly facial expressions (During & McMahon, 1991), even when verbal IQ is controlled for (Camras et al., 1990; Shenk, Putnam, & Noll, 2013). These latter findings are probably a consequence of altered functioning of neural systems associated with the processing of facial emotion (Curtis & Cicchetti, 2011; McCrory et al., 2013). Specifically, maltreated children tend to misattribute anger (Camras, Sachs-Alter, & Ribordy, 1996) and show elevated event-related potentials in response to angry faces (Cicchetti & Curtis, 2005). Findings concerning significant developmental delay in the emotional understanding of maltreated young children are quite consistent (Pears & Fisher, 2005), if somewhat reduced, when IQ and socioeconomic status are controlled for (Smith & Walden, 1999).[4] Understanding sad and angry emotions at age 6 predicts social competence and social isolation at age 8 (Rogosch, Cicchetti, & Aber, 1995). There have also been reports of delayed ToM understanding in maltreated children (Cicchetti et al., 2003; Pears & Fisher, 2005), and studies suggest that the capacity to parse complex and emotionally charged representations of the parent and of the self may even deteriorate with development (Toth, Cicchetti, Macfie, Maughan, & VanMeenen, 2000). Stein, Fonagy, Wheat, Kipp, and Gerber (2004), testing a heterogeneous sample, showed that mentalizing, as measured by the AAI Reflective Functioning (RF) Scale, fully accounted for the relationship between childhood maltreatment and impairment in adult romantic relationships. Similarly, Taubner and Curth (2013) showed the RF Scale to fully mediate the relationship between experiences of abuse and aggressive behavior in 97 adolescents aged between 15 and 18 years. Chiesa and Fonagy (2014), in a study of 234 individuals drawn from a clinical PD group ($n = 112$) and one demographically matched nonpsychiatric group ($n = 122$) using a shared battery of measures, which included the SCID-II, the Symptom Checklist-90-R and the AAI (used to assess RF levels), found RF to be a mediator between childhood adversity, PD, and symptom distress. A comprehensive systematic review (Macintosh, 2013) identified five studies (Bouchard et al., 2008; Fonagy & Bateman, 2006b; Fossati et al., 2009; Fossati, Feeney, Maffei, & Borroni, 2011; Stein & Allen, 2007) providing support for the assumption that mentalizing mediates the relationship between attachment or adversity and adult functioning. However, more research is clearly needed in this area.

We will review the evidence for impairments in different aspects of mentalizing in detail. It is sufficient here to say, however, that evidence that directly connects maltreatment, trauma, and mentalizing capacities in BPD patients is also still relatively limited. Yet, importantly, BPD patients have been found to exhibit high levels of alexithymia (i.e., impairments in mentalizing with regard to the self) and have difficulty in describing their affect in

[4]The appropriateness of controlling for IQ is not entirely clear given that IQ itself will also reflect social and emotional deprivation (see, e.g., Crandell & Hobson, 1999).

social situations (New et al., 2012), both of which have been related to trauma. In samples where the majority of patients report early trauma, patients manifest amygdala hyperreactivity in response to social stimuli combined with blunted subjective appraisal of these stimuli (Hazlett et al., 2012; Minzenberg, Fan, New, Tang, & Siever, 2007). Ghiassi et al. (2010) reported more impaired cognitive ToM performance on the Happe Cartoon Picture Story Task in BPD patients with lower self-reported parental care during childhood, frequent maternal punishments, and lengthy periods of separation. PTSD intrusions and sexual trauma have been shown to be negatively related to performance on the Movie for the Assessment of Social Cognition (MASC; Preissler et al., 2010). Furthermore, 58% of patients in this study reported sexual assault by a known assailant, which was associated with further impairment in mental state attributions. Only around half of these patients had a comorbid diagnosis of PTSD, suggesting that trauma, rather than PTSD, was responsible for the impairment in mentalizing. Dyck et al. (2009) provided tentative data that traumatized patients with BPD were most likely to show dysfunctional emotion recognition. Dziobek et al. (2011) showed that there was less activation in the superior temporal sulcus and superior temporal gyrus (STS/STG)—brain areas involved in mentalizing (see below)—in BPD patients with increased levels of intrusive traumatic memories.

Indirect support was also provided by a longitudinal study of 1,100 twins in the United Kingdom, showing that extreme scores on borderline symptoms in early adolescence were predicted by poor ToM scores at age 5, independently of IQ, and by early behavioral and affective indicators of mental health problems specifically in families characterized by a history of mental ill health (Belsky et al., 2012).

Considered in relation to attachment, mentalizing deficits associated with childhood maltreatment may be a form of decoupling, inhibition, or even a phobic reaction to mentalizing: (1) adversity may undermine cognitive development in general (Cicchetti, Rogosch, & Toth, 2000; Crandell & Hobson, 1999; Stacks, Beeghly, Partridge, & Dexter, 2011); (2) mentalizing problems may reflect arousal problems associated with exposure to chronic stress (see Cicchetti & Walker, 2001); and (3) the child may avoid mentalizing to avoid perceiving the abuser's hostile and malevolent thoughts and feelings about him or her (e.g., Fonagy, 1991; Goodman, Quas, & Ogle, 2010). These are all potential problems that will have a significant negative impact on a child's psychological, emotional, social, and educational development.

Maltreatment can contribute to an acquired partial mind-blindness by compromising open, reflective communication between parent and child. Maltreatment may undermine the benefit derived from learning about the links between internal states and actions in attachment relationships (e.g., the child may be told that he or she deserves, wants, or even enjoys the abuse to which he or she is being subjected). This is more likely to be harmful if the maltreatment is being perpetrated by a family member. Even in cases when maltreatment is taking place outside the home, the parents' ignorance of it may invalidate the child's communications with the parents about his or her feelings. In such a situation the child finds that reflective discourse does not correspond to his or her feelings, a consistent misunderstanding that could reduce the child's ability to understand and mentalize verbal explanations of other people's actions. In such circumstances, the child is likely to struggle to detect the mental states behind actions, and will tend to see these actions as inevitable rather than intended.

Taken together, these speculations clearly imply that the foundations of subjective selfhood will be less robustly established in those who have experienced early neglect. Such individuals will find it more difficult to learn about how subjective experiences inevitably vary between people. As we have seen, in some longitudinal investigations, low parental affection or nurturing in early childhood appears to be more strongly associated with elevated risk for borderline, antisocial, paranoid, and schizotypal PDs than physical or sexual abuse in adolescence (Afifi et al., 2011; Gao, Raine, Chan, Venables, & Mednick, 2010; Hengartner, Ajdacic-Gross, Rodgers, Muller, & Rossler, 2013; Johnson, Cohen, Kasen, Ehrensaft, & Crawford, 2006; Powers, Thomas, Ressler, & Bradley, 2011; Tyrka et al., 2009; Widom et al., 2009), pointing to the importance of neglect, low parental involvement, and emotional maltreatment. But this is just part of the picture.

There is an emerging view that apparent impairment of cognition as a consequence of early adversity could be more appropriately seen as a tendency favored by natural selection for development to optimize the child's adaptation to his or her social context, even given the challenges posed by the social context (Blair & Raver, 2012; Frankenhuis & Panchanathan, 2011). The anomalies of mentalization associated with adversity reviewed above can as readily be considered to be an atypical specialization as an impairment (Frankenhuis et al., 2013). We have previously suggested that there is likely to be a considerable cost to children contemplating the mental state of adults who hold malevolent and hostile intentions toward

them; in such circumstances it may be preferable to forgo reflective considerations, particularly of the cognitions of others (Fonagy, 1991). This speculation is consistent with an evolutionary-developmental view that suggests that we have to study the likely impact for survival and the costs and benefits (to children) of developing particular mental capacities in particular social contexts (Belsky, 2012; Ellis et al., 2012). Here, we want to emphasize the idea of a common final pathway: all these types of adversity seem to cause impairments in mentalizing that may bring benefit to the child under some social conditions, but in normal adult contexts tend to render the individual more vulnerable—even in the face of social adversity in adulthood. The precise nature of these impairments largely depends on the way individuals initially attempt to deal with experiences, which becomes increasingly generalized: they tend to use either predominantly attachment hyperactivating strategies, predominantly attachment deactivating strategies, or, in more severe cases, attachment disorganization, a combination of hyperactivating and deactivating strategies. Studies reviewed earlier show that the first and third strategies are most often used by BPD patients, and that attachment deactivating strategies are used not only in the context of disorganized attachment but also by most BPD patients in certain interpersonally challenging circumstances. In the next section, we review these strategies and their influence on mentalizing in more detail.

SECONDARY ATTACHMENT STRATEGIES, MENTALIZING, AND THE NEUROBIOLOGY OF BPD

Neurobiology of Stress, Attachment, and Mentalizing

Having summarized the emergence of mentalizing impairments in the course of development, we are in a better position to understand the specific mentalizing impairments of BPD patients. Beyond a general impact of attachment disruptions on mentalizing, secondary attachment strategies have a more specific influence on mentalizing in BPD and may explain individual differences in the expression of BPD and specific mentalizing profiles, in accordance with the evidence reviewed earlier in this chapter that BPD is markedly heterogeneous with respect to attachment status and mentalizing impairments. We argue that recent neuroscientific findings may further help us understand the intrinsic relationships among attachment experiences, mentalizing, and affect regulation.

Earlier formulations (e.g., Fonagy & Bateman, 2006b; Fonagy & Target, 2006) proposed that, at extreme levels, the activation of the attachment system is associated with a deactivation of mentalizing along with other emotion-induced cognitive dysfunction (e.g., Krause-Utz et al., 2012). Following the model outlined by Arnsten and colleagues (Arnsten, Mathew, Ubriani, Taylor, & Li, 1999) and Mayes (2000, 2006), we now suggest that with increased arousal there is a switch from cortical to subcortical systems, from controlled to automatic mentalizing, and, subsequently, to nonmentalizing modes (see Figure 17.2), with first evidence showing that activation in the neural network underpinning mental state decoding is reduced as a result of exposure to attachment-related stress (Nolte et al., 2013).

Two points are critical for understanding impairments in mentalizing in this context. First, owing to the neurochemical switch associated with escalating levels of emotional stress, patterns of brain functioning can shift from flexibility to automaticity: that is, from relatively slow executive functions mediated by the prefrontal cortex (PFC) to faster habitual behaviors mediated by posterior cortical (e.g., parietal) and subcortical (e.g., amygdala, hippocampus, and striatum) structures. At the same time, mentalizing seems to disappear as self-protective physical reactions (i.e., fight–flight–freeze) begin to dominate behavior. This has the presumed evolutionary value of promoting immediate adaptive responses to danger. In situations of interpersonal stress, however, where complex cognitive-emotional functioning (i.e., mentalizing) may be helpful, the loss of mentalizing may be a significant inconvenience, to say the least. Thus, the degree of arousal generated by interpersonal situations is critical. More generally, there will be situational variations when social stress triggers the threshold for switching from executive (mentalizing) to automatic (fight–flight–freeze) responding. We also assume, following Arnsten et al. (1999), Mayes (2000), and Nolte et al. (2013), that the threshold for switching can be lowered as a result of exposure to early stress and trauma of the type that has been documented for BPD patients, as described earlier in this chapter.

Second, both situational and more stable within-person variations play a role in the switch from more controlled to automatic mentalizing. This may also be a domain in which genetic as well as developmental influences make themselves felt. In particular, research suggests that in BPD, stress regulation, mediated by the hypothalamic–pituitary–adrenal (HPA) axis, is disturbed (Jogems-Kosterman, de Knijff, Kusters, & van Hoof, 2007; Nater et al., 2010; Scott, Levy, & Granger, 2013; Wingenfeld, Spitzer, Rullkotter, & Lowe, 2010). Functional magnetic resonance imaging (fMRI) studies of BPD patients in which the background

level of stress and/or attachment system activation was manipulated (e.g., Minzenberg et al., 2007) confirm the abnormal pattern of frontal deactivation and associated hyperresponsiveness of the limbic system in a range of contexts, using situational induced stress (Kraus et al., 2010) and in studies of the moderating influence of trait arousal (Holtmann et al., 2013; see reviews by Mier et al., 2013; Salavert et al., 2011). For example, Silbersweig et al. (2007) reported that under conditions of negative emotion and behavioral inhibition, BPD patients showed relatively decreased ventromedial PFC (vmPFC) activity, including medial orbitofrontal and subgenual anterior cingulate cortex (ACC), and increased amygdalar–ventral striatal activity correlating with decreased constraint. Further, findings with implications for the function of the HPA axis have confirmed that BPD patients with an explicit trauma history show a reduction in pituitary size (Garner et al., 2007), elevated levels of corticotropin-releasing hormone in cerebrospinal fluid (Lee, Geracioti, Kasckow, & Coccaro, 2005), dysfunctions of cortisol responsivity (Jogems-Kosterman et al., 2007; Minzenberg, Grossman, et al., 2006; Walter et al., 2008), and disturbed dexamethasone suppression test responses (Wingenfeld et al., 2007).

Although these studies require further replication in view of several methodological limitations, including small sample sizes, disparate experimental paradigms, and considerable heterogeneity in sample selection (e.g., comorbidity with depression, childhood abuse, PTSD and coping styles; Fertuck et al., 2006; Kahl et al., 2006), research to date has provided considerable evidence that the activation and deactivation of the attachment system is closely linked to arousal and stress regulation (Heinrichs & Domes, 2008; Lieberman, 2007; Mayes, 2006). Studies on rodent models and neuroimaging studies have shown that the activation of the attachment system underpinning both caregiving and partner preference is associated with the activation of two related systems that have consistently been shown to play an important role in promoting and maintaining attachment behavior: (1) the dopaminergic reward-processing system (Champagne et al., 2004; Strathearn, Li, Fonagy, & Montague, 2008); and (2) the oxytocinergic system (Levine, Zagoory-Sharon, Feldman, & Weller, 2007; Prossin, Love, Koeppe, Zubieta, & Silk, 2010). The functioning of the oxytocinergic system provides an obvious account for the replicated association between attachment security and the developmental acquisition of mentalizing competencies (Heinrichs, von Dawans, & Domes, 2009). Vasopressin may play an analogous role, perhaps especially in males (Atzil, Hendler, Zagoory-Sharon, Winetraub, & Feldman, 2012; Caldwell, Lee, Macbeth, & Young, 2008; Gouin et al., 2012; Young & Hammock, 2007). Oxytocin facilitates empathic facial recognition and in-group trust (Bakermans-Kranenburg & van IJzendoorn, 2013), it increases perceived salience of social cues (Shamay-Tsoory et al., 2009), and it improves empathic accuracy in less socially proficient individuals (Bartz et al., 2010), including improving altruistic behavior in individuals with relatively higher right frontal activity (Huffmeijer, Alink, Tops, Bakermans-Kranenburg, & van IJzendoorn, 2012) (the emotional empathic approach recruits mainly left frontal areas). By enhancing activity in the insula and inferior frontal gyrus, it improves understanding of others' emotions, and it reduces anxiety by decreasing amygdalar activity, facilitating contingent responses of help and compassion (Bakermans-Kranenburg & van IJzendoorn, 2013).

Yet the effects of oxytocin are influenced by situational and interindividual differences (Bartz, Zaki, Bolger, & Ochsner, 2011). Research suggests that attachment history moderates the effects of oxytocin as well as the setting of the switch that turns the mentalizing system from planned, controlled, and organized cognition to automatic processing with narrowed, poorly sustained attention, and increased vigilance for attachment disruptions such as rejection and abandonment (Cullen et al., 2011; Kamphausen et al., 2013). For example, Gillath, Bunge, Shaver, Wendelken, and Mikulincer (2005) reported an fMRI study of women with high and low scores on attachment anxiety and avoidance who were asked to either think about or stop thinking about various relationship scenarios. When thinking about negative scenarios, women with high levels of attachment anxiety showed more activation in the hippocampus (a brain region associated with memory retrieval), anterior temporal pole, and dorsal ACC (dACC) (emotion-related regions), and less activation in the orbitofrontal cortex. It seems that in contemplating negative scenarios, individuals with an anxious attachment style may under-recruit areas of the brain associated with emotion regulation, and show enhanced retrieval of negative memories. In a prospective study, Strathearn and colleagues (Strathearn, Fonagy, Amico, & Montague, 2009; Strathearn et al., 2008) examined whether differences in the attachment security of 30 first-time mothers, assessed using the AAI before the birth of their child, were related to brain reward and peripheral oxytocin responses to infant cues. Approximately 10 months after the birth of the child, mothers viewed images of either their own infant's smiling and crying face or smiling/crying faces of other infants, while being fMRI scanned. Securely attached mothers showed greater activation of brain reward regions,

including the ventral striatum, and the oxytocin-associated hypothalamus/pituitary region. The mothers' peripheral oxytocin response during infant contact was also significantly higher in securely attached mothers, and the size of change from baseline oxytocin levels was positively correlated with brain activation in response to the mothers' own infants in both regions. Important differences based on attachment history emerged when the mothers viewed their infants' crying faces: securely attached mothers continued to show greater activation in reward-processing regions, while insecure/dismissing mothers showed deactivation of the reward system and insular activation, congruent with findings described earlier. Activation of the insula may be associated with feelings of unfairness, pain, and disgust (see review by Montague & Lohrenz, 2007). Mothers with insecure/dismissing attachment histories appeared less able to down-regulate the sad feelings evoked in them by their infant's crying faces, possibly because they felt overwhelmed by sad memories of their own past. These findings suggest that for securely attached mothers, infant cues (whether positive or negative in affect) may act as an important affective signal of incentive salience (Berridge, 2007), reinforcing and motivating responsive maternal care. However, insecurely attached mothers may experience a negative subjective reaction that would make them reflect (mirror) their infant's sadness without being able to create a symbolic/mentalizing distance between their infant's state of mind and their own.[5]

The finding of reduced reward activation in mothers with insecure/dismissing attachment is also consistent with a study of responses to smiling adult faces and positive task feedback (Enzi et al., 2013; Vrticka, Andersson, Grandjean, Sander, & Vuilleumier, 2008). This study reported a negative correlation between dismissing attachment scores and activation of the ventral striatum. This is congruent with the typical distant and detached relational style of avoidant individuals, and their tendency to deny the importance of attachment relationships. In both studies, challenges to the attachment system yielded greater ventral striatal activation in securely attached individuals, while in avoidant/dismissing individuals it was associated with a relative down-regulation of reward-related activity.

[5]The phenomenon of insecure mothers experiencing and therefore perhaps mirroring their infant directly, rather than in a marked (nearly, but clearly not, the same) manner, may be one of the mechanisms behind the intergenerational transmission of patterns of attachment (van IJzendoorn & Bakermans-Kranenburg, 1997).

Consistent with the above claims about the complementary activation of the attachment and mentalizing systems, in the study of Vrticka et al. (2008), avoidant attachment was positively correlated with activation in the medial PFC (mPFC) and the ventral ACC—areas that have been implicated in controlled social cognition and mentalization, social rejection, and emotion suppression. Moreover, Vrticka et al. (2008) reported that secure attachment was positively correlated with activation of the ventral striatum in response to positive reinforcement, but negatively related to activation of the amygdala in response to negative reinforcement (Hazlett et al., 2012). This is in line with our previous suggestions that secure attachment requires the simultaneous (and paradoxical) activation of components that are normally reciprocally activated—mentalizing and reward salience-associated regions of the brain (Fonagy & Bateman, 2006b). These observations are also congruent with the assumption that secure attachment consists of a combination of low anxiety and low avoidance.

Importantly, these findings also suggest that we can expect to see differences in the quality of mentalizing depending on the quality of the relationship within which this aspect of interpersonal cognition is observed (Allen et al., 2008). This is congruent with the view that internal working models of attachment relationships may be to a large extent relationship-specific (Fraley, 2007; Overall, Fletcher, & Friesen, 2003), as evidenced by substantial within-person variation in internal working models of attachment (e.g., father vs. mother; see, e.g., Fraley, 2007; Pierce & Lydon, 2001). Similarly, mentalizing capacities are not invariant across different relationships. This assumption is also borne out by findings that general and relationship-specific mentalization, although overlapping, can be distinguished (Happé & Frith, 1996; Humfress, O'Connor, Slaughter, Target, & Fonagy, 2002; O'Connor & Hirsch, 2001). Further, key aspects of mentalizing, such as feelings of trust and fairness, are relationship-specific (Bugental & Johnston, 2000; Fiddick & Cummins, 2007). Perhaps the best evidence for the relationship-specific nature of mentalizing comes from studies on parental mentalizing (for a review, see Sharp & Fonagy, 2008), showing distinct features of mentalizing with regard to one's infant (Luyten, Mayes, Nijssens, & Fonagy, 2015; Rutherford, Goldberg, Luyten, Bridgett, & Mayes, 2013; Slade, 2005), and from studies suggesting interactions among therapist levels of mentalizing and mentalizing capacities in patients (Diamond, Stovall-McClough, Clarkin, & Levy, 2003; Diamond & Yeomans, 2008; Prunetti et al., 2008; Vermote et al., 2009).

Secondary Attachment Strategies and Mentalizing

On the basis of these and other findings, we thus propose that a combination of characteristics strongly associated with attachment history is likely to determine whether an individual switches in a particular context from more controlled, reflective to automatic mentalization (Figure 17.2; see Fonagy & Luyten, 2009; Luyten, Fonagy, Lowyck, et al., 2012, for a detailed discussion).

Studies reviewed suggest that *anxious-preoccupied attachment strategies*, which are, as noted, characteristic of many BPD patients, are associated with simultaneously lowered thresholds for attachment system activation and controlled mentalizing deactivation. Thus, more automatic, subcortical systems, including the amygdala, have a low threshold for responding to stress in BPD patients. This could offer a comprehensive explanation for one of the central dynamic features of BPD patients, that is, their tendency to form attachments easily and quickly, often resulting in many disappointments. This pattern would be due to their low threshold for activation of the attachment system and their low threshold for deactivation of neural systems associated with controlled social cognition, including systems involved in judging the trustworthiness of others (Fonagy & Bateman, 2006b). The vicious interpersonal cycles that are so characteristic of many BPD patients can thus be understood in terms of excitatory feedback loops leading to increased vigilance for stress-related cues in anxious attachment, particularly attachment characterized by high anxiety and high avoidance (Mikulincer & Shaver, 2007). These cycles are also related to BPD patients' hypervigilance concerning emotional states in others and their failure to deactivate their tendency to emotionally resonate with these states, which in turn feeds into their lack of self–other differentiation, setting up a likely sequence of further failures in understanding their own internal world, that of others, and the relationship between the two.

We assume that the arousal of the attachment system, beyond more general interpersonal stress-induced arousal, brings with it a general loss of mentalizing. Any trauma arouses the attachment system (in seeking for protection), and attachment trauma may do so chronically. In the situation where a child is seeking proximity to a traumatizing attachment figure as a consequence of trauma, he or she may, naturally, be further traumatized. The prolonged activation of the attachment system may be an additional problem, as the arousal of attachment may have specific inhibitory consequences for mentalizing over and above that which might be expected as a consequence of increased emotional arousal. It is therefore possible that in BPD the inhibition of mentalizing may not just be accounted for by trauma-related rapid triggering of the fight–flight system, but, more specifically, the hyperactivation of the attachment system characteristic of BPD may be a consequence of maltreatment specifically in an attachment context. Attachment theorists, in particular Mary Main and Erik Hesse, have suggested that maltreatment leads to disorganization of the child's attachment to the caregiver because of the irresolvable internal conflict created by the need for reassurance from the very person who also (perhaps by association, if the caregiver is not themselves the maltreater) generates an experience of lack of safety (Hesse & Main, 2000). Activation of the attachment system by the threat of maltreatment is followed by proximity seeking, which drives the child closer to an experience of threat, leading to further activation of the attachment system (Hesse, 2008). This conflict leaves the child with an overwhelming sense of helplessness and hopelessness and leads to what has been considered a hyperactivation of the attachment system. There is no resolution of the anxiety; looking for reassurance and protection generates more fear through the (mental) proximity of the maltreating figure. The ready triggering of the attachment system in BPD may be a residue of trauma history and manifests as both the rapidly accelerated tempo of intimacy in interpersonal relations and vulnerability to the temporary loss of mentalizing.

In contrast, in individuals with *secure attachment*, activation of the attachment system predictably involves a relaxation of normal strategies of interpersonal caution. There is good evidence that intense activation of the neurobehavioral system underpinning attachment is associated with deactivation of the arousal and affect-regulation systems (Fonagy & Luyten, 2009; Luyten, Fonagy, Lowyck, et al., 2012), as well as the deactivation of neurocognitive systems likely to generate interpersonal suspicion, that is, those systems and brain regions involved in social cognition or mentalizing, including the lateral PFC (LPFC), mPFC, lateral parietal cortex (LPAC), medial parietal cortex (MPAC), medial temporal lobe (MTL), and rostral ACC (rACC; Bartels & Zeki, 2000, 2004; Lieberman, 2007; Nolte et al., 2013; Satpute & Lieberman, 2006; Van Overwalle, 2009). For example, with increased intimacy, regions of the brain associated with reflective mentalizing will be deactivated. This is congruent with expressions in many languages that associate love with various forms of sensory handicaps, particularly blindness.

Moreover, as noted, the neuropeptides oxytocin and vasopressin play key roles in two aspects of creating attachment relationships: (1) by activating the reward/attachment system; and (2) by deactivating neurobehavioral systems that are involved in mediating social avoidance (Bartels & Zeki, 2004). For instance, oxytocin and vasopressin have been shown to inhibit aversion of both female and male rodents to infant pups, as well as promoting a number of affiliative behaviors, including caregiving behavior (Heinrichs et al., 2009; Insel & Young, 2001). Oxytocin also reduces behavioral and neuroendocrine responses to social stress, and seems to enable animals to overcome their natural avoidance of proximity and to inhibit defensive behavior, thereby facilitating approach behavior (Simeon et al., 2011). Vasopressin has primarily been implicated in male-typical social behaviors, including aggression and pair-bond formation, and mediates anxiogenic effects (Heinrichs & Domes, 2008). Thus, in the context of secure attachment, the activation of the attachment system will generate increased experience of reward, increased sensitivity to social cues, and decreased social avoidance, but also the potential for the reward to override lack of trust. This complex set of associations with social behavior may help to account for the puzzling combination of facilitative and inhibitory associations between attachment history and social cognition. For instance, in two separate imaging studies, Bartels and Zeki (2000, 2004) reported that the activation of areas mediating maternal and/or romantic attachments appeared simultaneously to suppress brain activity in several regions mediating different aspects of cognitive control, including those associated with making social judgments and mentalizing. The medial prefrontal, inferior parietal and medial temporal cortices, mainly in the right hemisphere, as well as the posterior cingulate cortex, may be part of the specialized neurocircuitry for attention and long-term memory (Cabeza & Nyberg, 2000), perhaps specifically responsible for integrating emotion and cognition (e.g., emotional encoding of episodic memories; Maddock, 1999) and subserving mood-mediated inhibition or enhancement of cognitive processing (Mayberg et al., 1999). The second set of brain areas observed to be deactivated by the activation of attachment concerns included the temporal poles, temporoparietal junction (TPJ), amygdala, and mPFC—areas consistently linked to explicit and internally focused mentalizing, including judgments of social trustworthiness, moral judgments, ToM tasks, and attention to one's own emotions.

BPD patients also tend to use *attachment deactivating strategies* in some contexts in an attempt to deal with increasing levels of arousal and affect dysregulation. Attachment deactivating strategies have been shown to keep the neural systems involved in controlled mentalization online for longer, including systems involved in judging the trustworthiness of other individuals (i.e., the pull mechanism associated with attachment; Vrticka et al., 2008). Yet, whereas securely attached individuals are able to keep the controlled mentalizing system online even in the context of increased stress, meaning that the attachment system is less likely to be triggered, the deactivating strategy of dismissive individuals is likely to fail. If securely attached individuals are those who are able to retain a relatively high activation of prefrontal areas in the presence of activation of the dopaminergic mesolimbic pathways (the attachment and reward system), then differences in mentalization between securely attached individuals and those individuals who primarily rely on attachment deactivating strategies may become apparent only under increasing stress; this seems consistent with the findings of experimental studies (Mikulincer & Shaver, 2007).

By contrast, a low threshold for the stress-induced activation of the attachment system may translate as a low threshold for overriding of distrust. In addition, we hypothesize that, if all other factors are constant, the greater an individual's use of hyperactivating strategies, the lower will be their threshold for the activation of automatic mentalizing, and thus the stronger the relationship between stress and a switch to automatic mentalizing will be (Figure 17.2; Fonagy & Luyten, 2009; Luyten, Fonagy, Lowyck, et al., 2012). Moreover, we predict that greater use of hyperactivating strategies will also be associated with an increased time to recovery of mentalizing, while secure attachment (and perhaps deactivating) strategies might be associated with relatively rapid recovery of the capacity for mentalizing (Mikulincer & Shaver, 2007), but these predictions largely remain to be investigated.

However, this model would explain why mentalizing deficits in BPD are more likely to be observed in experimental settings that trigger the attachment system, such as in studies collecting AAI narratives (e.g., Fonagy et al., 1996; Levinson & Fonagy, 2004), and also why BPD patients who mix deactivating and hyperactivating strategies, as is characteristic of *disorganized attachment*, show a tendency for both hypermentalization and failure of mentalizing. On the one hand, because attachment deactivating strategies are typically associated with minimizing and avoiding affective content, BPD patients often have a tendency for hypermentalization, that is, continuing attempts to mentalize, but without integrating cognition and affect. On the

other hand, as the use of hyperactivating strategies is associated with a decoupling of controlled mentalization, this leads to failure of mentalizing as a result of over-reliance on models of social cognition that antedate full mentalizing (Bateman & Fonagy, 2006b). Similar conclusions have been drawn from an fMRI study in BPD patients in which Thematic Apperception Test cards elicited hyperactivation of the ACC and mPFC, suggesting an overly sensitive switch between emotionally salient and neutral information processing (Schnell, Dietrich, Schnitker, Daumann, & Herpertz, 2007).

Finally, it is important to note that BPD is in some ways at the opposite end of the spectrum from *interpersonal resilience* (Gunderson & Lyons-Ruth, 2008; Higgitt & Fonagy, 1992). Understanding the association between resilience and mentalizing also provides helpful insight into BPD (Fonagy & Target, 1997). Studies suggest that the ability to continue to mentalize even when under considerable stress leads to so-called broaden and build (Fredrickson, 2001) cycles of attachment security, which reinforce feelings of secure attachment, personal agency, and affect regulation (build) and lead one to be pulled into different and more adaptive environments (broaden) (Mikulincer & Shaver, 2007). Congruent with these assumptions, studies on resilience have shown that positive attachment experiences are related to resilience in part through relationship recruiting, that is, the capacity of resilient individuals to become attached to caring others (Hauser, Allen, & Golden, 2006). Hence, high levels of mentalizing and the associated use of security-based attachment strategies when faced with stress are good candidates to explain the effect of relationship recruiting and resilience in the face of stress. In contrast, attachment hyperactivation and deactivation strategies have been shown to limit the ability to broaden and build in the face of stress. Moreover, they have also been shown to inhibit other behavioral systems that are involved in resilience, such as exploration, affiliation, and caregiving (Insel & Young, 2001; Mikulincer & Shaver, 2007; Neumann, 2008). This may also partially explain these individuals' difficulties in entering lasting relationships (including relationships with mental health care professionals) and the intergenerational transmission of borderline pathology.

To summarize, we may thus envisage three types of association between aspects of social cognition and attachment. These are created by (1) attachment relationships based upon intense romantic or maternal love; (2) attachment relationships based upon threat/fear; and (3) secure and predictable attachment relationships. Although any given attachment relationship may have features of each of these three types, they are important to distinguish, as the relationship between attachment activation and mentalizing may differ considerably depending on which feature is activated within an attachment relationship. First, mediated by dopaminergic structures of the reward system in the presence of oxytocin and vasopressin, the love-related activation of the attachment system can inhibit the neural systems that underpin the generation of negative affect. Second, threat-related activation of the attachment system (e.g., triggered by perceived threat, loss, or harm) may also evoke intense arousal and overwhelming negative affect, bringing about an activation of posterior cortical and subcortical areas and switching off frontal cortical activity, including mentalizing (Arnsten et al., 1999; Arnsten, 1998; Mayes, 2000). Third, meanwhile, a secure and predictable attachment relationship may be most effective in *preempting* threat, which possibly reduces the need for frequent activation of the attachment system.

The Multiple Vectors of Mentalizing

We are now in a better position to understand the often seemingly conflicting evidence on mentalizing in BPD, with enhanced capacities for accurate identification often matched by inferior performance in other settings. This lack of consistency has been well documented and suggested to be linked to characteristics of the interaction situation (Dinsdale & Crespi, 2013). In our view, the main reasons for these conflicting findings are that mentalizing is a multidimensional capacity, and BPD patients are characterized by specific impairments in mentalizing capacity, while other aspects of mentalizing are not impaired or are even more highly developed than in nonclinical controls. The literature on social cognition in BPD (e.g., Ripoll, Snyder, Steele, & Siever, 2013; Roepke, Vater, Preissler, Heekeren, & Dziobek, 2012; Thoma et al., 2013) is difficult to interpret without contemplating the disorder as characterized by what we have termed a specific *mentalizing profile*, and thus results of studies on social cognition in BPD depend on the participants' engagement in the task, the level of arousal the experiment evokes, and the individuals' dominant attachment strategy primed by the context of the study or experiment. Further, as mentalizing is a multicomponent capacity made up of a normally finely balanced set of complementary competencies or vectors, inadequate mentalizing can, paradoxically, manifest as superior mentalizing because dysfunction in one pole of a vector will cause the other pole to manifest in the absence

of normal moderation if the task used to assess mentalizing calls for only one of the two poles of paired competencies.

Over the years, we have come to distinguish four vectors of mentalizing: (1) cognitive–affective; (2) internal–external; (3) automatic–controlled; and (4) self–other. Here, we review research concerning impairments in these different vectors of mentalizing in BPD and the typical mentalizing profile associated with BPD (Figure 17.1). In each section, we discuss relevant research (see also Table 17.1 for a summary).

Cognitive Versus Affective Mentalizing

The most commonly made developmental and neuroscientific distinction in relation to mentalizing is between *cognitive* and *affective* content. One pertinent formalization of this distinction was suggested by Baron-Cohen and colleagues (Baron-Cohen, Golan, Chakrabarti, & Belmonte, 2008), who identified two independent processing systems that might normally be charged with parsing these categories of content: (1) the ToM mechanism (TOMM), which mediates agent-attitude proposition representations (or M-representations) such as "Mother – believes Johnny – took the cookies"; and (2) the empathizing system (TESS), which uses self-affective state proposition representations (or E-representations) such as "I am sorry – you feel hurt – by what I said." The latter are labeled self-affective state propositions because TESS is constrained always to create representations where emotion in the other is consistent with the self-affective state. Thus, it will not create "I am pleased that you are in pain" because it has to be a state that the self can generate in relation to the presumed state in the other (a constraint that may not be present in psychopaths; Blair, 2008). A phrase such as "I am pleased that you are in pain" feels wrong at many levels because the attribution of affect originates from self-experience and, as one would not feel pleased to be in pain, attributing pleasure in this connection sounds almost ungrammatical (unless one has antisocial tendencies).

In relation to affect, propositions are appropriately grounded in self-state; conversely, in relation to cognition, the assumption that just because I *assume* something to be the case, it must *be* the case is inappropriate. The logic of agent-attitude propositions separates physical reality from belief by allowing a belief to be true while at the same time being incompatible with the reality to which it links (e.g., "I believe you had bagels for breakfast" may be a true statement in relation to one's beliefs—that is, it is what I believe—but is incompatible with your having had fruit salad for breakfast, rather than bagels).

Emotion understanding and belief-desire reasoning normally interact, and only in combination do they generate genuine social understanding in what we have termed *mentalized affectivity* or the feeling of feeling (Fonagy et al., 2002; Jurist, 2005). Full mentalizing involves the integration of both *cognitive* knowledge (dominated by agent-attitude propositions) and *affective* knowledge (dominated by inferences drawn from one's own feelings, i.e., self-affective state propositions).

Agent-attitude propositions are probably subserved by several areas within the PFC, particularly cortical midline structures, while self-affective state propositions appear to be more likely to be processed by a more automatic, embodied, and lateralized system including parts of the vmPFC (Sabbagh, 2004; Shamay-Tsoory, 2009; Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory, Aharon-Peretz, & Levkovitz, 2007). The latter structure may be particularly important as TESS and TOMM representations come to be integrated, but it is currently not known how these two systems might function together to generate what we experience as empathy. Thus, ToM, from the neurobiological perspective, seems to recruit two independent (but interacting) systems, based on a neuroanatomical distinction within the mPFC. Cognitive ToM, which primarily concerns the processing of information about others' beliefs, is supported by dorsomedial PFC (dmPFC) activity. Affective ToM, which is an emotional form of mentalizing, cognitively inferring others' emotions, entails vmPFC activity. It should be noted that while this obviously overlaps with an emotion-focused empathy system, it is not the same as actually *feeling* the other's feeling (i.e., emotional empathy). Affective ToM is closer to being able to *imagine* affect (Gweon, Dodell-Feder, Bedny, & Saxe, 2012; Shamay-Tsoory, 2011).

Deficit in Understanding Beliefs. We may expect a young person to find difficulty in developing a strong capacity for processing the belief states of others if the behavior of their parent(s) is unpredictable (see, e.g., Helgeland & Torgersen, 2004). An early study by Arntz and Veen (2001) reported less complexity in BPD patients' character descriptions after watching a series of emotional and nonemotional film sequences. Veen and Arntz (2000) used short video clips from commercial movies and found that BPD patients made more extreme evaluations than controls with Cluster C PD diagnoses, but only when the themes concerned topics likely to generate emotional arousal in the patients. In a more recent study (Arntz & ten Haaf, 2012) involving evaluation of telephone discussions, BPD patients displayed more extreme evaluations compared with Cluster C

TABLE 17.1 Mentalizing Strengths and Impairments in BPD Across the Four Vectors

	BPD < comparison	BPD = comparison	BPD > comparison	
Cognitive (agent-attitude propositions)	Self-reported cognitive empathy reported lower (Harari, Shamay-Tsoory, Ravid, & Levkovitz, 2010; Ritter et al., 2011) Understanding Faux Pas test: show impaired cognitive understanding (Harari et al., 2010) Multifaceted Empathy Test: show cognitive empathy deficits, with less activation in the STS/STG regions in an fMRI study (Dziobek et al., 2008)	Happe Strange Stories Test: show no marked deficit in cognitive mentalizing (Arntz, Bernstein, Oorschot, & Schobre, 2009)	Heightened sensitivity to emotional cues (Lynch et al., 2006), especially in case of anger and fear (Domes et al., 2009; Wagner & Linehan, 1999) Superiority in attributing mental states on the basis of emotional cues (Franzen et al., 2011)	**Affective (self-affective state propositions)**
Mental interior (internally) focused	Deficits in making mental state judgments of others based on mental interiors, such as social exchange tasks (King-Casas et al., 2008; Unoka, Seres, Aspan, Bodi, & Keri, 2009) Studies of resting-state disconnectivity suggest abnormal default mode network (which has internal mentalizing as its function) connectivity in BPD (Saxe, 2006; Wolf et al., 2011)	Equal performance in Reading the Mind in the Eyes Test (Preissler et al., 2010; other studies have found BPD superiority in this area, see next column)	Stronger activation of visual processing when viewing negatively valenced pictures (Koenigsberg, Siever, et al., 2009) Hypersensitive to facial expressions (Domes et al., 2006; Lynch et al., 2006) Higher sensitivity to nonverbal communication (Frank & Hoffman, 1986; Ladisich & Feil, 1988) Better at Reading the Mind in the Eyes Test (Fertuck et al., 2009), or at least as good as clinically normal subjects (Preissler et al., 2010; Schilling et al., 2012) More likely to view characters/behaviors as negative or aggressive (Barnow et al., 2009); to have an impaired view of neutral faces in the context of anger or disgust (Daros, Zakzanis, & Ruocco, 2013); and to react with hostility to neutral social interactions (Domes et al., 2008)	**External cue focused**
Conscious, deliberate, reflective	Dramatically reduced reflective mentalizing ability in the context of attachment relationships (Fischer-Kern et al., 2010; Fonagy et al., 1996; Gullestad, Johansen, Hoglend, Karterud, & Wilberg, 2013) Poorer results in the MASC test (Preissler et al., 2010; Ritter et al., 2011; Sharp et al., 2011)	Able to perform experimental mentalizing tasks relatively well under low arousal (Arntz et al., 2009)	Superiority in inferring others' intentions (Ladisich & Feil, 1988) Better at perceiving and responding to small social cues relating to fairness (Franzen et al., 2011) Self-report tests: BPD patients more able to predict others' self-ratings (Ladisich & Feil, 1988)	**Implicit, automatic, nonconscious, immediate**
Relies on explicit mental state attributions to other, (inhibits shared representation); relies on mental state attribution system in empathy tasks	Severe impairment in ability to differentiate self from other (Barnow et al., 2005; Bender & Skodol, 2007; Blatt & Auerbach, 1988; Fuchs, 2007) Mental state attribution system, which relies on symbolic, abstract processing of others' mental states, is impaired (Fonagy & Luyten, 2009; Ripoll et al., 2013) Decreased activity in superior temporal sulcus during deliberate empathic processing (Dziobek et al., 2011; Mier et al., 2013) Decreased activation of medial prefrontal cortex during regulation of aggression (New et al., 2009) Hyperactivation of the medial prefrontal cortex in response to rejection (Ruocco, Medaglia, Tinker, et al., 2010)		Greater susceptibility to emotional contagion, overwhelmed by others' affect (Fonagy & Luyten, 2009; Ripoll et al., 2013) Hyperreactive response to both positive and negative emotional stimuli in the amygdala (Hazlett et al., 2012; Minzenberg et al., 2007), and when attempting to regulate responses to negative cues (Koenigsberg, Fan, et al., 2009) Anterior insula more aroused in affective empathy tasks (Dziobek et al., 2011) Higher conflation of bodily experiences (Allen et al., 2008) Difficulty in decoupling their representations of others from self-representations (Bender & Skodol, 2007)	**Relies on shared self-other representations; reliance on shared representation system in empathy tasks**

patients; Arntz and colleagues label this *multidimensional dichotomous thinking*.

The Happe Strange Stories Test revealed no marked deficit in cognitive mentalizing (Arntz et al., 2009), and another version of this higher order ToM test also showed no difference in performance on the part of BPD patients (Ghiassi et al., 2010). Yet, in this latter study, performance was associated with lower quality parental care (maternal punishment and lengthy separation) during childhood, supporting our hypothesis concerning the negative impact of an adverse early environment on the development of mentalizing. Moreover, on the Understanding Faux Pas test, in which the participant is asked to detect a social faux pas in each story they are presented with, BPD patients were shown to have impaired cognitive understanding but intact affective appreciation (Harari et al., 2010).

On self-reported empathy based on the Interpersonal Reactive Index, BPD patients have been reported to score significantly lower on cognitive empathy (Dziobek et al., 2011; Guttman & Laporte, 2000; Harari et al., 2010; New et al., 2012; Ritter et al., 2011). The more recently developed Multifaceted Empathy Test (MET) (Dziobek et al., 2008) also showed BPD patients to have cognitive empathy deficits associated (in an fMRI study) with less activation than controls in the STS/STG regions. Notably, this reduction was associated with the increased likelihood of intrusive traumatic memories. The MET consists of photographs depicting people in emotionally charged situations and is intended to produce strong emotional reactions in the subject. Thus, the test assesses cognitive empathy but under an emotional charge.

Heightened Sensitivity Toward Emotional Experience. Several studies have shown that patients with BPD respond with heightened sensitivity toward any kind of emotional cue (Lynch et al., 2006); this is particularly marked in the case of anger (Domes et al., 2009) and fear (Wagner & Linehan, 1999). There is accumulating evidence that, in the presence of emotional cues, patients with BPD may outperform nonclinical controls in attributing mental states to interaction partners (Franzen et al., 2011).

The literature on emotional intelligence in BPD is split. Some studies (Gardner, Qualter, & Tremblay, 2010; Hertel, Schutz, & Lammers, 2009) show reduced emotional intelligence. By contrast, Beblo et al. (2010) found no difference, and Park et al. (1992) claimed evidence of enhanced emotional intelligence. As the construct of emotional intelligence itself links poorly to mentalization, it may be best simply to set aside these ambiguous findings. Interestingly, increasing the cognitive load—in other words, not allowing the emotional processing to have priority over outputs and increasing the complexity of the task—removes the advantage of BPD patients and even creates apparent impairment (Dyck et al., 2009; Minzenberg, Poole, & Vinogradov, 2006b). We would argue that the impact of cognitive load on performance indicates a cognitive deficit that serves to abolish the emotional processing advantage normally experienced by BPD patients in the absence of such a load.

One hypothesis to account for emotional hyperactivity assumes a combination of amygdala overactivation and orbitofrontal cortex and PFC regulatory deficits (Domes et al., 2009). Self-reported measures of emotional empathy are sometimes (Ritter et al., 2011) but by no means always (Dziobek et al., 2011; Harari et al., 2010) shown to be lower in BPD patients. While this may seem contrary to the argument we propose here of heightened sensitivity to emotion in the absence of a cognitive counterbalance, it seems to us to be counterintuitive to expect patients with BPD to have accurate introspective capacity in relation to their functioning in the absence of adequate deliberate reflective competence, and we question, along with others (see also Dziobek et al., 2011), the validity of these self-ratings.

Mentalizing Based on Internal Versus External Features of Self and Others

The heightened sensitivity to emotional experiences in BPD seems to be intrinsically related to an increased sensitivity to external features of self and others as a source of knowledge about mental states. The focus of attention for making imaginative inferences about both our own and others' states of mind can be internal or external and, accordingly, different neural networks appear to be involved (Lieberman, 2007). The focus in mentalizing can be on one's *self* (including one's embodied experiences, i.e., embodied mentalizing) or on *others*, but ideally a balance is struck between the two. In creating mental models of mental states we can focus on *external* reactions of others (e.g., their facial expressions) or make indirect inferences based on more complex computations about their *internal* processes—that is, what they might be feeling or thinking in a given situation given what we know about their past behavior and the situation at hand.

A focus on mental interiors means directly considering thoughts, feelings, and experiences, and is accompanied by the activation of a medial frontoparietal network (Satpute & Lieberman, 2006). Converging functional imaging evidence supports the notion that the default mode network (DMN) is specifically related to self-referential activity and is only minimally involved in the processing of external stimuli (Buckner, Andrews-Hanna, & Schacter, 2008). The

DMN is a resting-state network assumed to have as one of its functions internal mentalizing detached from external stimuli (Smith et al., 2009). Focusing mentalization on exteriors—on physical and visible features or actions of one's own or another's actions—appears to recruit a more lateral frontotemporoparietal network. As the mental interior may be thought of as a second-order representation of the exterior (Fonagy et al., 2007a), the internal/external distinction applies as much to self- as to other-related mentalizing.

Problems in Internal Cue-Focused Mental State Understanding. Studies clearly suggest that BPD patients primarily show deficits in making mental state judgments when these call for a direct focus on mental interiors. For example, when King-Casas et al. (2008) asked BPD patients to engage in a neuroeconomic social exchange task, they found that these patients had difficulty in anticipating the likely impact of their actions on a partner player they had not met before. In particular, they were poor at coaxing their partner (i.e., generating a good feeling in the partner about the collaboration). These findings were replicated by Unoka, Seres, Aspan, Bodi, and Keri (2009), who showed that BPD patients transferred smaller amounts of money when playing the role of investor in a multiple-round trust game. More recently, studies of resting-state disconnectivity in BPD (Wolf et al., 2011) suggest that patients with BPD have abnormal DMN connectivity, particularly in the left frontopolar cortex (FPC) and insula; the former in particular is linked to the processing of intentional thoughts, self-referential information, and interpersonal interactions (Saxe, 2006). The FPC has been shown to exhibit abnormal levels of activation during the experience of social exclusion (Ruocco, Medaglia, Ayaz, & Chute, 2010). However, the task-independent resting-state connectivity anomaly suggests that internally directed attention in BPD patients has diminished importance. The same study revealed a correlation between increased resting-state connectivity of the insula (which has been related to the perception and monitoring of somatosensory and affective internal states) and symptoms of dissociation (Lanius et al., 2005). Taken together, the findings confirm an absence of balance and connection between internal and external experience in BPD patients.

Superiority in External Cue-Focused Mental State Understanding? Processing mental states from external cues is likely to be phylogenetically older as well as less controlled and reflective. Increased vigilance in relation to external indicators of negative attitudes may be highly adaptive in social situations of childhood, where early recognition of these indicators could help the child to avoid and even preempt threat, rejection, or brutal attack, as discussed earlier in this chapter.

We assume that, when *not* moderated by context-activated cues related to the observed person's internal state, individuals with BPD may be more accurate in mental state understanding than non-BPD controls based on external features. Koenigsberg et al. (2009) noted a stronger activation of visual processing in borderline patients, relative to healthy controls, during the processing of negatively valenced emotional pictures, which was associated with stronger amygdala activation. The weight of evidence suggests that mentalizing tasks that focus attention on external features cause fewer problems for these patients, and BPD patients have actually been found to be hypersensitive to facial expressions (e.g., Domes et al., 2008; Lynch et al., 2006; Schulze, Domes, Koppen, & Herpertz, 2013; but see Matzke, Herpertz, Berger, Fleischer, & Domes, 2014; Mier et al., 2013).

An elegant test of judging mental states by external cues is the widely used Reading the Mind in the Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Studies have shown the performance of BPD patients to be either better than normal (Fertuck et al., 2009; Frick et al., 2012; Scott, Levy, Adams, & Stevenson, 2011 for negative emotions) or the same as healthy controls (Preissler et al., 2010; Schilling et al., 2012). Fertuck et al.'s findings echo demonstrations showing exceptional sensitivity to nonverbal (external) cues on the part of BPD patients (Frank & Hoffman, 1986; Ladisich & Feil, 1988). Further, as noted, substantial trauma may be an important moderator here: trauma has been related to hypervigilance to emotional states, but lower levels of accuracy in mental state attribution (Fertuck et al., 2009; Roepke et al., 2012).

In the *absence* of a contextual counterpoint of putative internal states, tiny behavioral cues, coupled with a general negative stance (fueled by current and past negatively valenced interpersonal interactions), are likely to lead BPD patients to identify indications of negative intentions in the actions and demeanor of others who are, in fact, neutral. As an example of this, Barnow et al. (2009) presented short silent video clips of individuals simply entering a room and sitting down. BPD patients saw the characters more negatively and as more aggressive than both MDD patients and healthy controls. If impairment of facial affect recognition is reported, it is evident primarily for neutral faces when anger or disgust is encountered (Daros et al., 2013). BPD patients also give more hostile evaluations of normal social interactions (Domes et al., 2008).

Implicit–Automatic Versus Explicit–Controlled Mentalizing

From the mentalizing perspective, BPD is characterized by an overreliance on automatic or implicit mentalizing. *Automatic* mentalizing refers to fast, parallel, reflexive processes that require little consciousness or effort, whereas *controlled* or explicit mentalizing involves more conscious, deliberate, and serial reflective processes. While different situations might call for more immediate nonreflective or more contemplative deliberate mentalizing, the overemphasis of either intuition or contemplation would clearly reflect poor-quality mentalizing in most circumstances (Frith & Frith, 2012; Lieberman, 2007; Nosek, Hawkins, & Frazier, 2011; Payne & Gawronski, 2010; Satpute & Lieberman, 2006; Uddin, Iacoboni, Lange, & Keenan, 2007).

Explicit mentalizing is typically interpreted, conscious, verbal, and reflective. It is a serial and slow process that requires attention, intention, awareness, and effort. By contrast, automatic or implicit mentalizing is perceived, nonconscious, nonverbal, and unreflective. It presumes parallel (and therefore much faster) processing, is reflexive, and requires little effort, focused attention, or intention (Satpute & Lieberman, 2006). Developmentally, nonverbally determined implicit mentalizing appears to be robust early in the second year of life (Baillargeon, Scott, & He, 2010) or perhaps earlier (Kovacs et al., 2010), while verbal recognition of another's perspective is reliable only in the fourth year (Carpendale & Lewis, 2006) or even later, perhaps after age 8 (Gweon et al., 2012). Different brain areas may be recruited for automatic and controlled mentalizing (Keysers & Gazzola, 2006, 2007). Automatic social cognition involves the amygdala, basal ganglia, vmPFC, lateral temporal cortex (LTC), and dACC—in general phylogenetically older brain circuits that rely heavily on sensory information. By contrast, controlled mentalizing recruits the LPFC, mPFC, LPAC, MPAC, MTL, and rACC, which are phylogenetically newer brain circuits involved in the processing of linguistic and symbolic material.

Deficit in Conscious, Deliberate, Reflective Mentalizing. Mentalizing in real time under realistic contextual demands requires the capacity to consciously and deliberately reflect on and make accurate attributions about the emotions, thoughts, and intentions of others, and to display an accurate and balanced appreciation of a social situation. Such a capacity has been repeatedly demonstrated to be suboptimal in BPD patients. In what was perhaps the first demonstration of the failure of reflective mentalizing in BPD, Fonagy et al. (1996) showed a dramatically reduced ability of BPD patients to reflect on their own and others' mental states in the context of attachment relationships; this deficit in RF has been shown to be reversible by psychotherapy (Levy et al., 2006). The findings on RF have been replicated by two relatively large studies (Fischer-Kern et al., 2010; Gullestad et al., 2013). A number of studies have shown BPD patients to be impaired on the MASC, which is currently probably the most valid and reliable measure of this aspect of mentalizing (Preissler et al., 2010; Ritter et al., 2011; Sharp et al., 2011). The MASC is a video-based test of mentalizing requiring participants to recognize the mental state of characters as they interact in an everyday life group scenario involving relationships. The misinterpretation of interpersonal situations because of limited reflective capacity may generate extreme and inappropriate emotions in social interactions (Dziobek et al., 2011), particularly in combination with an overemphasis on externally oriented social cognition.

Increased arousal could further disrupt the possibility of effective higher order cognitive function. Arousal has indeed been shown to increase automatic mentalizing and inhibit neural systems associated with controlled mentalizing (Lieberman, 2007; Mayes, 2006). As discussed earlier, BPD patients tend to have a lower threshold for the activation of these fight–flight arousal systems (Jogems-Kosterman et al., 2007), although this association may be more complex than it appears (Kahl et al., 2006). Abnormal stress regulation and the developmental and neurological separation of these two systems may explain how emotional arousal in BPD might on the one hand cause the loss of explicit mentalizing, but on the other hand allow for particularly accurate implicit attunement to the states of mind of individuals around them (i.e., externally based mentalizing). By the same token, individuals with BPD may be able to perform experimental mentalizing tasks relatively well under low arousal (Arntz et al., 2009), but they cannot explain the states of mind they experience under high arousal, and show confusion about such mental states because they are dominated by reflexive assumptions about the internal states of others. Unfortunately, psychotherapists of many orientations often attempt to provide mentalistic understandings for issues that trigger intense emotional reactions (e.g., challenging interpersonal situations, issues of shame, guilt, feelings of inadequacy) at a time when the patient's capacity for effective explicit mentalizing is practically inaccessible (Fonagy & Bateman, 2006a).

Superior Intuition and the Borderline Empathy Paradox. Contrary to the assumption of a general social-cognitive deficit in BPD, clinical observations (Carter & Rinsley, 1977; Krohn, 1974) had already drawn attention to an interpersonal hypersensitivity in this group of patients. This was confirmed by investigations using sensitivity to nonverbal communication cues as criteria (Frank & Hoffman, 1986). Dinsdale and Crespi (2013) reviewed 28 studies of empathic functioning in BPD in an attempt to resolve the so-called empathy paradox. They report that in about half the studies, mentalizing—assessed in terms of levels of empathy—is enhanced in BPD. They particularly note the superiority of BPD patients in tasks that call for inference of others' intentions (as in Ladisich & Feil, 1988), or perceiving and responding strategically to small social cues indicating fairness (Franzen et al., 2011). In an ingenious study, Ladisich and Feil (1988) assessed the perception of other people's feelings and personality by comparing individuals' self-ratings with personality ratings made by others (BPD patients, non-BPD patients, and psychiatrist expert raters). The ratings made by BPD patients matched self-ratings better than those of non-BPD patients, indicating higher empathy among the BPD patients, although they did not quite manage to outperform the expert raters. The experience of borderline empathy is familiar to most clinicians suddenly struck by a remarkably insightful comment by their BPD patient.

Mentalizing with Regard to Self Versus Others

Finally, what about mentalizing about the self versus others in BPD? Social-cognitive theories of BPD focus primarily on deficits in social cognition with regard to others. Yet neuroscience studies suggest surprising parallels between the developmental and brain processes underpinning how the self and others are understood in mental state terms (Lieberman, 2007; Uddin et al., 2007). From a mentalizing perspective, given the dialectic nature of the emergence of the capacity to mentalize, such an intimate connection is to be expected. This is also in line with theories suggesting that in BPD the capacity to differentiate between the self and the other is severely impaired (e.g., Barnow et al., 2005; Bender & Skodol, 2007; Blatt & Auerbach, 1988; Fuchs, 2007; Kernberg, 1975, 1984). We have argued that such identity diffusion is created by an absence of a sense of agency, which reflects a more general failure of mentalization—the continuity of our sense of self is normally ensured via our sense of a connection between intentional mental states and actions (Bolton & Hill, 1996; Fonagy, 1991).

The common brain circuitry used in mentalizing self and other may explain the difficulty of the normally developing child to acquire a sense of selfhood and may, perhaps more importantly, also explain BPD patients' struggle to free themselves from the undue influence of others' mental states. The neuroimaging literature suggests that two distinct neural networks are used in self-knowing and knowing others (Lieberman, 2007; Uddin et al., 2007), and BPD patients may show a marked imbalance between these two systems (Fonagy & Luyten, 2009). Ripoll et al. (2013) suggested distinguishing these two systems as follows: the *shared representation* (SR) system, in which empathic processing relies on shared representations of others' mental states; and the *mental state attribution* (MSA) system, which relies more on symbolic and abstract processing. This distinction overlaps with those suggested by Shamay-Tsoory (2011) and others (Dimaggio, Lysaker, Carcione, Nicolo, & Semerari, 2008; Lieberman, 2007; Lombardo, Barnes, Wheelwright, & Baron-Cohen, 2007; Uddin et al., 2007).

The SR system entails a visceral recognition of the experience of others without high-level cognitive processing, based on a similarity of neural activation while experiencing and observing others experiencing states of mind (Lombardo et al., 2010). It is assumed to be a more body-based, frontoparietal mirror-neuron system that is involved in understanding the multimodal embodied self (e.g., face and body recognition) and understanding others through motor-simulation mechanisms (Gallese, Keysers, & Rizzolatti, 2004; Rizzolatti & Craighero, 2004; Van Overwalle & Baetens, 2009). This suggests that a fundamental process allowing us to appreciate the actions and emotions of others involves the activation of the mirror neuron system for actions and the activation of visceromotor centers for the understanding of affect (Lombardo et al., 2010). This is thought to be one of the key evolutionary mechanisms underpinning social empathy—knowing from the inside, as it were, how another feels. Hence, this is an implicit, automatic system, providing physical other-to-self and self-to-other mapping, allowing the immediate understanding (but also misunderstanding, as we shall see) of self and others. SR processing is present from infancy and phylogenetically dates back to rodents. Neuroanatomically, it engages the inferior frontal gyrus, inferior parietal lobule (both of these zones are rich in mirror neurons; Bernhardt & Singer, 2012; Van Overwalle & Baetens, 2009), anterior insula, and ACC (both of which are involved in observed and felt pain). Seyfarth and Cheney (2013) argue that trust, empathy,

and sensitivity to others' emotional states develops out of a largely unconscious mimicking tendency, which we share with primates and which plays a key role in affiliative behavior (van Baaren, Holland, Kawakami, & van Knippenberg, 2004). Seyfarth and Cheney provide primate data to suggest that this subconscious, reflexive appreciation of others' intentions and experience has substantial selection advantages and potentially forms the basis of complex forms of mentalizing because natural selection favored individuals who were motivated to empathize with others. Neurochemically, it is linked to oxytocinergic functioning (Hurlemann et al., 2010). The SR system provides for motor empathy, underpins shared pain, and explains emotional contagion, as well as rudimentary recognition of intention and emotional states (Shamay-Tsoory, 2011).

While SR processing dominates early development (Decety & Michalska, 2010), because automatic mirroring inevitably generates distress in response to others' distress, a further neural development is needed to supplement it, based on a cortical midline system consisting of the vmPFC and dmPFC, the TPJ and the medial temporal pole (Lieberman, 2007; Uddin et al., 2007). This system is less bodily based, and processes information about the self and others in more abstract and symbolic ways (Frith & Frith, 2006; Uddin et al., 2007). The system also appears to be mainly shaped across development by interpersonal relationships, is phylogenetically initially found in primates, emerges fully in adolescence, and is neurochemically strongly linked to dopaminergic functioning (Lackner, Bowman, & Sabbagh, 2010). Behaviorally, this explicit MSA network underpins perspective taking and both cognitive ToM (involving the dmPFC) and affective ToM (underpinned by the activity of the vmPFC). It is important to note that cognitive inference of affect is an act of imagination that is not the same as feeling another's feelings, which SR processing entails (Gweon et al., 2012).

The SR and MSA systems may be mutually inhibitory (Brass & Haggard, 2008; Brass, Ruby, & Spengler, 2009; Brass, Schmitt, Spengler, & Gergely, 2007), which in our opinion further elucidates typical features of BPD. Neuroimaging studies indicate that the neural regions most often recruited in the inhibition of imitative behavior are those involved in explicit mental state attributions. If, as we have suggested, the MSA-based system is impaired in BPD, these individuals may experience an excessive and developmentally inappropriate activation of the SR system, leaving them with difficulties in decoupling their representation of another person's experience from their self-representations (Fonagy & Luyten, 2009; Ripoll et al., 2013), which leads to an overemphasis on others' feelings and emotions (emotional contagion) and, in turn, to confusion about the self (identity diffusion and feelings of inner emptiness), as well as an undue emphasis on externally oriented mentalizing ("jumping to conclusions") that is difficult to modulate.

Deficit in the MSA System. Decreased activity has been noted in the STS of patients with BPD during deliberate empathic processing (Dziobek et al., 2011; Mier et al., 2013). Decreased activation of the mPFC was noted during the regulation of provoked aggression (New et al., 2009), which may indicate an inadequate perspective-taking stance on the part of these patients. Similarly, a task calling for the use of psychological distancing from affective stimuli failed to demonstrate higher activation in the posterior cingulate cortex for BPD patients (Koenigsberg, Fan, et al., 2009). Dysfunction may also be indicated by hyperactivation (hypermentalizing) of the mPFC in response to an experience of rejection (Ruocco, Medaglia, Tinker, et al., 2010), an important finding, as BPD has been associated both with hypomentalizing and hypermentalizing, particularly in the context of tasks involving complex interpersonal relationships (Sharp et al., 2011).

Inappropriate Activation of the SR System. Amygdala hyperreactivity has been shown in individuals with BPD in response to both positive and negative stimuli (Hazlett et al., 2012; Mier et al., 2013; Minzenberg et al., 2007), as well as in attempts by patients to regulate their response to negative social cues (Koenigsberg, Fan, et al., 2009). Ripoll et al. (2013) cite unpublished data suggesting a lack of habituation indicated by amygdala activity associated with limitations in subjective perception of social support. The anterior insula has also been shown to be hyperreactive during affective empathy tasks. Dziobek et al. (2011) reported that during emotional empathy the right mid-insula was more strongly activated in individuals with BPD than in nonclinical controls. This anatomical region is associated with bodily arousal (Simmons et al., 2013), suggesting that an emotional empathy task engages BPD patients more than controls. In support of this speculation, a positive association between right mid-insula activation and skin conductance was shown for this patient group. One interpretation of the finding reported by King-Casas et al. (2008) is that BPD patients' mistrustful reactions to fair offers in a multi-round social exchange task were due to insula hyperreactivity.

A more complex account may be necessary to explain the fairly consistent finding that patients with BPD appear to be less responsive in terms of facial cues than nonclinical controls. For example, Herpertz et al. (2001) found

that male criminal offenders with BPD showed less facial response to emotionally arousing stimuli than normal controls. Similar observations were made by Renneberg et al. (2012) for female BPD patients watching films with both positive and negative emotional valence. Lobbestael and Arntz (2010) showed abuse-related films to BPD patients and also found reduced facial response. Finally, in a carefully conducted investigation, Staebler et al. (2011) found that BPD patients reacted with more mixed emotions in a social exclusion paradigm, but not with greater expressed affect, as may be expected. At first glance, these findings of reduced emotional expression appear to contradict the claim of overactive SR processing. However, the masking of expression on the part of these patients may be a learned response to an internally exaggerated response (see above), which, these patients have learned, is required of them to maintain adequate social interactions. The observed dissociation between internal experience (as receiver of social signals) and external expression (as sender of signals) might be a further expression of a disturbed relationship between emotional processing mechanisms (Roepke et al., 2012). Only further research including multiple measures of (physiological) arousal can shed further light on these findings, particularly as dissociations between stress channels have often been noted, suggesting marked impairments in stress regulation (Luyten, Van Houdenhove, Lemma, Target, & Fonagy, 2013).

The sharing of structures to reflect on the self and others not only implies a model for acquisition but also highlights the potential for conflating the embodied simulation of another person's experience with one's own experience. As mentioned already, despite some contrasting findings, such conflations of bodily experience often appear to occur in BPD (Allen et al., 2008). Developmentally, we tend to assume a state of egocentrism in children—that they are limited to interpreting the world from their own point of view (Piaget & Inhelder, 1948/1956). However, motor neuron findings suggest the opposite: that infants have to develop the capacity to learn what is "me" as distinguished from states of mind assumed to be shared by others. So how does the child learn to differentiate self from others?

Work by Marcel Brass and colleagues has offered a suggestion about how these two apparently independent systems that process representations of self and other may interact to create an experience of "not-me" and therefore, by extension, an experience of "me" (Brass, Derrfuss, Forstmann, & von Cramon, 2005; Brass & Haggard, 2008; Brass et al., 2007). The theoretical claim that self and other representations are shared and are the default mode of the motor system is, as we have seen, reasonably well supported. People have a tendency to mirror actions automatically. This causes interference with voluntary actions when the observed action of another is incongruent with the intended act. Studies have shown that observing an action has a powerful influence on movement execution: being shown an image of a congruent action results in the subject initiating the movement themselves more quickly, while observing an image of an incongruent action interferes with execution of the movement (e.g., Kilner, Paulignan, & Blakemore, 2003; Ramsey, Cumming, Eastough, & Edwards, 2010). For example, if participants are asked to lift their middle finger while observing the experimenter lift his or her index finger at the same time, their reaction times will be extended. Interference from incongruent observed actions appears to be particularly powerful when the observed action is seen as intentional (Bouquet, Shipley, Capa, & Marshall, 2011; Liepelt, Cramon, & Brass, 2008) and when the intent is perceived—even without the movement being performed (Liepelt et al., 2009).

Neuroimaging studies indicate that the neural regions that are most often recruited in the inhibition of such imitative behavior are the anterior frontomedial cortex (aFMC) and the TPJ area (Brass et al., 2005; Derrfuss, Brass, Neumann, & von Cramon, 2005)—in other words, the cortical areas that are also related to mentalizing, self-referential processing, and self-agency. The TPJ is involved in perspective-taking (e.g., Aichhorn, Perner, Kronbichler, Staffen, & Ladurner, 2006; Ruby & Decety, 2003), sense of agency (e.g., Decety & Grezes, 2006; Kuhn, Brass, & Haggard, 2013; Spengler, von Cramon, & Brass, 2009; Sperduti, Delaveau, Fossati, & Nadel, 2011), and mentalizing (Frith & Frith, 2006). The aFMC is involved in mentalizing (Fonagy & Luyten, 2010; Frith & Frith, 2006; Gilbert et al., 2007) and self-referential processing (Northoff et al., 2006). In fact, work by Brass's group suggests that there is a functional relationship between the extent to which an individual can inhibit imitative behavior and his or her capacity for belief-desire reasoning (Brass et al., 2007, 2009). Thus, it appears that the inhibition of imitative behavior involves cortical areas that are also related to mentalizing, self-referential processing, and determining self-agency.

In summary, knowing oneself and knowing others are two capacities clearly connected both developmentally and in terms of the brain structures subserving these processes. This applies to both symbolic and automatic ways of knowing. Congruent with the mentalizing approach, this overlap—in terms of both ontogeny and neural circuits—points to the interpersonal origins of the self, which

experiences itself and other selves as motivated by mental states (Cicchetti & Toth, 2009; Hobson, 2002; Rochat, 2009). This also sheds further light, in our opinion, on the strong impact of experiences of separation and rejection in BPD patients. These experiences become more understandable if we assume that the real or symbolic disappearance of the attachment figure is experienced as catastrophic because the individual feels exposed to a direct and unmediated experience of vulnerability to others' reactions, necessarily fragmented and impossible to differentiate from phenomenological self-experience. In such a nonmentalizing mode, the self is experienced in a psychic equivalence mode: the other and the self are experienced as being the same. The self can emerge only when it is able to know that it is *not* the other person. This leads us to a discussion of similar nonmentalizing modes of experiencing subjectivity; what happens when the capacity for (controlled) mentalizing is lost?

Reemergence of Nonmentalizing Modes in BPD

The capacity for mentalizing and the associated capacities for affect representation, affect regulation, and attentional control normally obscure forms of experiencing subjectivity that developmentally antedate the capacity for full mentalizing. These nonmentalizing modes allow us to better understand some intriguing features of BPD phenomenology and the aforementioned findings concerning BPD and the dimensions of mentalizing:

1. In the *psychic equivalence mode*, thoughts and feelings become too real and internal experience acquires the compelling power of external reality. There is a suspension of the experience of doubt, and individuals increasingly believe that their own perspective is the only one possible. This state reflects the domination of the propositional logic of emotion states (where reality is defined by self-experience) over the propositional logic of cognition (where agent-attitude propositions permit knowledge that belief is independent of reality; Baron-Cohen et al., 2008).
2. In the *teleological mode*, there is a focus on observable goal-directed behavior and objectively discernible events that may potentially constrain these goals. The individual cannot accept anything other than a modification in the realm of the physical as a true index of the intentions of the other. This reflects an extreme exterior focus in the mentalizing profile and a momentary loss of controlled, reflective, deliberate mentalizing.
3. In the *pretend mode*, thoughts and feelings become severed from reality (resulting in hypermentalizing or pseudomentalizing[6]), which, in the extreme, may lead to feelings of derealization and dissociation. As noted, these features of BPD are—in our opinion quite inappropriately given their prevalence and role (Luyten, Fonagy, Lowyck, et al., 2012; Sharp et al., 2011)—neglected in research and theoretical conceptualizations of this condition. Ideas form no bridge between inner and outer reality; the mental world is no longer fully coupled with external reality. This reflects explicit mentalizing being overridden by implicit mentalizing, such that there is excessive internal focus unchecked by references to external indicators, poor belief-desire reasoning, and vulnerability to fusion with others' identity and a tendency to become lost in the complexity of the world of beliefs and desires with which physical reality is only loosely coupled. The common consequence is hypermentalizing, where groundless inferences are made about mental states, sometimes reminiscent of confabulation. Hypermentalizing can arise because the failure to mentalize generates challenging interpersonal encounters that in turn produce stress, drawing the individual away from appropriately considering the social context. This creates schematic rudimentary models of belief states that are inappropriately enriched by poorly grounded inferences about mental states, generating further interpersonal difficulties and stress. These limitations of mentalizing generate increasingly desperate attempts to make sense of what may be occurring in the interpersonal domain.

As we mentioned earlier, the prementalizing modes are often accompanied by a pressure to externalize unmentalized alien-self parts. We assume that these discontinuities in self-experience (when the person feels aspects of their self-experience to be of themselves or their own, yet also to be alien to their self-experience) generate a sense of incongruence, which is dealt with through externalizing (or projection)—behaving toward others as though the others own the unmentalized self-experiences and on occasions being successful in generating these experiences in them (Fonagy & Target, 2000).

[6]These are related tendencies to overproduce putative beliefs and desires in relation to others and to do so without reference to available contextual information, leading to the generation of excessively detailed images of internal states that do not correspond to what is genuinely experienced as real.

ADOLESCENCE AND THE EMERGENCE OF BPD

We have thus far covered the early origins of BPD, which are most likely rooted in interactions between genetic endowment and environmental factors, but this does not explain the full picture of BPD and its origins. One important and often neglected developmental phase remains to be discussed. This neglect is indeed remarkable for several reasons. First, although most major mental disorders, including BPD, first develop in adolescence, BPD pathology in adolescence is still underdiagnosed (Laurenssen, Hutsebaut, Feenstra, Van Busschbach, & Luyten, 2013). Second, we have seen that genetic factors may come to play an important role in determining attachment in adolescence (Fearon et al., 2013). Third, adolescence is also characterized by marked changes in cognitive function and these considerably influence mentalizing capacities. Specifically, adolescence is associated with dramatic changes in social cognition: it marks the beginning of the capacity to hold in mind multiple dimensions of a concept, enabling the ability to plan and to think about the implications of one's actions; cognitive control and executive functioning are greatly increased; and self-awareness, self-consciousness, and self-reflective capacities become a central focus of adolescents' self-experience (Steinberg, 2005). Recent studies of the development of mentalizing in adolescents, for instance, have shown that the capacity of young people to adopt others' perspectives improves substantially between 12.5 and 16.5 years, yet even at age 17 it is less than adults are capable of (Dumontheil, Apperly, & Blakemore, 2010).

The mentalizing approach to adolescence essentially proposes that those adolescents who have adequate capacity for mentalizing (and linked capacities of effortful control and attention) make considerable progress in their capacity to make sense of their own mind and the complexities of relationships during this developmental stage, leading to relatively stable, and essentially positive, feelings of identity (including sexual identity) and autonomy, and the capacity to enter into stable, differentiated interpersonal relationships (Blatt & Luyten, 2009; Fonagy & Luyten, 2011). Hence, adolescence may be associated with marked changes in attachment, which may partially result from genetic factors, changes in mentalizing capacities leading the adolescent to be pulled into different (interpersonal) environments, and interactions among these factors. This is not a linear process, however, and both research and clinical practice suggest that this process, even in normal development, is essentially characterized by (1) much trial and error and (2) hypomentalizing–hypermentalizing cycles, features that are typical of the typical storm and stress of adolescence.

These assumptions are supported by findings concerning brain development in adolescence, showing (1) increased numbers of brain connections (synaptogenesis), followed by synaptic pruning, which creates more efficient brain networks; and (2) axonal myelination, increasing the efficiency of neural transmission (Blakemore, 2008, 2010; Giedd, 2004). During adolescence, the PFC, which, as noted, plays a key role in mentalizing and self-regulation, undergoes pronounced structural reorganization, with brain grey matter (indicative of new synaptic connections being made) increasing in this region up to the onset of puberty. Importantly, it then shows a rapid decrease in density, which continues throughout adolescence into early adulthood, suggesting an increasing efficiency of processing through the pruning of unused connections. Further, the changes in the superior temporal cortex, including the second major center for representing mental states, the STS, are more protracted and do not follow the pattern in the PFC of a sharp inverted U-curve; rather, grey matter in the STS steadily *declines* during adolescence and well into adulthood, reaching maturity relatively late. At the same time, improved connectivity between nerve cells is indicated by an increase in cortical white matter density from puberty, throughout adolescence, and into adulthood. Thus, early adolescence is characterized by a decrease in mentalizing capacities followed by gradual improvement throughout later phases, underpinned by neurobiological changes in the brain systems implicated in mentalizing.

In our view, this fine tuning of cortical regions involved in mentalizing underpins the dramatically changed sense of identity (self) and relationships (others) with the emergence of pubertal sexuality. Greater sensitivity to emotional states, a greater centrality of self-conscious emotions (e.g., shame, embarrassment, guilt, pride), and greater emphasis on sexuality and aggression, in particular, puts mentalizing under considerable pressure by increasing arousal; this is further reinforced by peer pressure and the challenge to de-identify with attachment figures, involving the challenge to redefine the balance between autonomy and relatedness (Blatt & Luyten, 2009). Mentalizing, thus, is biased in adolescence because of an imbalance between neural circuits subserving mentalizing and a functionally more mature limbic region. Greater self-consciousness and the resulting increased social awareness also render adolescents more aware of the importance of succeeding in social situations

and the social costs of failure. Hence, imbalances in brain development might underlie both increased sensitivity to rejection in adolescence (Davey, Yucel, & Allen, 2008) and the inability to manage the implications of this increased awareness, expressed via hypermentalizing in an attempt to make sense of these experiences, alternating with hypomentalizing as a defensive strategy to avoid thinking about the painfulness of these experiences. A similar model may be suggested in relation to the development of executive functions (Hare et al., 2008), whereby the gradual development of prefrontal cognitive control mechanisms enables increased connectivity between prefrontal and limbic regions.

Whereas adolescence thus involves considerable challenges for adolescents with normal developmental histories, adolescents with a history of poor mentalizing are at even greater risk when faced with the typical social challenges that adolescence brings. Exaggerated experience of affect and limited capacities for affect regulation because of impairments in effortful and attentional control and mentalizing seriously impair the capacity to make sense of developmental changes in one's own mind, and in one's own mind in relation to others' minds. At the extremes, this may lead to feelings of identity diffusion and extreme hypomentalizing–hypermentalizing cycles, so typical of BPD patients. In our opinion, continuing attempts to make sense of one's own mind in relation to changing demands of others (e.g., parents, teachers, peers), leading to extreme pretend mode functioning (expressed in hypermentalizing), are a core feature of adolescents who are vulnerable for BPD. This assumption is congruent with studies reporting higher levels of both identity diffusion (Goth et al., 2012; Jung, Pick, Schluter-Muller, Schmeck, & Goth, 2013; Kassin, De Castro, Arango, & Goth, 2013; Westen, Shedler, Durrett, Glass, & Martens, 2003) and hypermentalizing (Sharp et al., 2011) in adolescents with (borderline) PD features.

These features seem to be intrinsically related to problems with increased self-consciousness and particularly shame, one of the most painful self-conscious emotions (Luyten, Fontaine, & Corveleyn, 2002). Indeed, a shame-prone self-concept has been related to BPD (Rusch et al., 2007), and a recent study suggests that a shame-prone self-concept was uniquely related to borderline personality features, and identity problems in particular, in middle childhood and adolescence (Hawes, Helyer, Herlianto, & Willing, 2013). These findings are congruent with our emphasis on a disturbed sense of identity and strong feelings of inner pain (Zanarini & Frankenburg, 2007) and toxic shame (Gratz et al., 2010; Levy et al., 2007; Rusch et al., 2007) as core features of BPD. Moreover, developmentally, these features are linked with marked interpersonal hypersensitivity (Gunderson & Lyons-Ruth, 2008) in adolescence. Rejection hurts, as is also evidenced by shared neural mechanisms of physical and psychological pain (Eisenberger, Lieberman, & Williams, 2003), and it seems that BPD patients have developed a heightened sensitivity to experiences of rejection, and thus inner pain, because of their inability to make sense of the pain associated with repeated feelings of shame and rejection. In many BPD patients, this vicious cycle seems to be increased by experiences of childhood abuse and neglect (Holm & Severinsson, 2008; Hopwood & Zanarini, 2012), which have also been shown to dysregulate pain-processing mechanisms (Luyten et al., 2013). Further, increased sensitivity to pain, which is also expressed in marked comorbidity between BPD and pain disorders (McWilliams & Higgins, 2013), coexists with blunting of pain sensations in BPD patients, probably as a consequence of repeated self-harm (Magerl, Burkart, Fernandez, Schmidt, & Treede, 2012; Pavony & Lenzenweger, 2014), providing further evidence for dysregulation of pain processing mechanisms in BPD. Moreover, findings of a blunted pain response are congruent with the earlier reported paradoxical finding of impaired expression of emotions but hyperreactivity to mental states in BPD patients.

Further, sexuality and aggression create additional challenges in adolescence, as psychoanalysts have long noted (Blos, 1962; Laufer & Laufer, 1984). Sexual excitement represents a special challenge to mentalizing, as the expression of infantile sexual feelings is among those rare infant emotion expressions that—at least to a certain extent—remain unmirrored even by the most sensitive of attachment figures (Fonagy, 2008). The hormone-driven emergence of psychosexuality in adolescence subsequently creates internal psychophysical experiences for the young person for which there is no adequate second-order representation, making action and enactment the preferred route for the expression of subjective experiences that are always, to a certain extent, alien to the self. This tendency to act out these alien-self parts (i.e., unmirrored experiences) in an attempt to come to grips with sexual urges is all the more problematic for adolescents vulnerable to BPD, given their problems with mentalizing, particularly for those adolescents with a history of sexual abuse. Risky sexual behaviors in BPD starting in adolescence have been well documented (Harned, Pantalone, Ward-Ciesielski, Lynch, & Linehan, 2011; Tull, Gratz, & Weiss, 2011), but what is important in our view is that these behaviors often tend to repeat victim–perpetrator cycles as expressed in

high rates of repeated sexual revictimization (Sansone, Chu, & Wiederman, 2011). Many of these adolescents have grown up in families with little mind-mindedness, and thus they often seem to completely lack the ability to make sense of their own mind and the minds of others, which, as noted above, renders them prone to acting out subjective experiences that cannot be mentalized, leading to impulsive behavior (e.g., externalizing symptoms, sexual promiscuity, self-harm). Alcohol or drugs might be used in an attempt to cope with these painful experiences of inner emptiness, pain, and confusion, and might function as a substitute for attachment relationships. These assumptions are supported by studies suggesting high rates of both risky sexual behavior and drug use in BPD patients (Harned et al., 2011; Tull et al., 2011). As noted, from a neurobiological perspective, attachment and addiction seem to be underpinned by the same neurobiology (Insel & Young, 2001).

In adolescents with a history of trauma, and sexual trauma and/or physical abuse in particular, feelings of sexuality and aggression are likely to pose a tremendous challenge, as, when confronted with these alien-self parts, such adolescents might feel a constant pressure to externalize these feelings, either by becoming involved in relationships in which they are abused or are the abuser, or by self-harm in an attempt to eradicate the feelings, or by a combination of these. Dissociation may also ensue in an attempt to get rid of intrusive memories and extensive rumination when in a pretend mode because it "drives them crazy." Moreover, in those who have abusive experiences, the close intertwining of sexuality and aggression puts their mentalizing abilities under increasing pressure. In these adolescents, feelings of love often lead, in a psychic equivalence mode, to the expectation that they will be abused, while conversely, the only way some of these adolescents may relate to others is by dominating and abusing them. Hence, feelings of love and desire may be easily confused with, and change into, primitive feelings of envy, jealousy, and rage, as emphasized in traditional (Klein, 1975) and more contemporary (Yeomans & Diamond, 2010) object-relational accounts of BPD.

Although the evidence in this area is less clear, destructive aggression (including envy and jealousy) may thus similarly be related to experiences of being unmirrored by early attachment figures. These experiences therefore remain without an internalized representation that the adolescent could use as a handle for regulation and control. In fact, a more general failure of representing changed body-states may characterize these adolescents. This may also explain the high comorbidity between BPD and functional somatic disorders (Luyten, van Houdenhove, et al., 2012) and eating disorders (Skårderud & Fonagy, 2012), as these disorders seem to reflect a failure of the mentalization of the ordinary events and experiences of life and a consequent representation of these in terms of bodily states. Particularly in eating disorders, major (bodily) changes seem to challenge mentalizing abilities, as these changes, together with other sociocultural expectations typical of this developmental phase (particularly for girls), herald the beginning of a major redefinition of the self, and of the self in relation to others. Although still speculative, these assumptions are supported by studies suggesting low levels of embodied mentalizing in patients with functional somatic disorders (Luyten, van Houdenhove, et al., 2012) as well as in those with eating disorders (Redondo, Luyten, & Estevez, 2015).

These considerations help us to understand not only the emergence of BPD in adolescence, but also its high comorbidity—particularly in adolescence—with externalizing problems (e.g., aggressive outbursts, risky sexual behavior), feelings of depression, eating disorder problems, substance abuse, and functional somatic complaints. They may also help us to understand the intricate relationship between a disturbed sense of identity and the profound interpersonal problems that characterize BPD, as they are both related to impairments in mentalizing (Luyten & Blatt, 2013), that is, the inability to make sense of the self in relation to others (and to make sense of others in relation to the self), leading to feelings of inner pain, emptiness, toxic shame, and, in the extreme, to dissociative experiences.

IMPLICATIONS FOR INTERVENTION

The MBT Approach

General Approach

Mentalization-based treatment (MBT) was initially developed in the 1990s for the treatment of adults with BPD, although it is now being applied to a range of disorders across the life span (see Bateman & Fonagy, 2012 for a representative set of therapeutic applications). The MBT approach is closely informed by our developmental perspective on the development of the social-cognitive functions—affect regulation; attentional control; the management of the dual arousal system involved in maintaining a balance between the mental functions undertaken by the anterior and posterior portions of the brain; and the capacity to mentalize—that are so necessary for healthy

interpersonal relations. Because these social functions develop in the context of early caregiver relationships, as well as genetic vulnerabilities, they are shaped by the individual's attachment experiences and, in particular, are vulnerable to the experiences of attachment trauma connected with childhood adversity. MBT, therefore, is rooted in attachment theory. It places mentalizing, within the attachment context, at the center of the therapeutic process. It is a therapy primarily defined not by a clustering of specific and related techniques but more by the *process that is stimulated in therapy*. At its core, MBT works through establishing an enduring attachment relationship with the patient while continuously stimulating a mentalizing process in the patient. Its aim is to develop a therapeutic process in which the mind of the patient becomes the focus of treatment. The objective is for patients to find out more about how they think and feel about themselves and others, how those thoughts and feelings influence their behavior, and how distortions in understanding themselves and others lead to maladaptive actions, albeit actions intended to maintain stability and manage incomprehensible feelings (more detail on the MBT model can be found in Allen et al., 2008; Bateman & Fonagy, 2006a; Bateman & Fonagy, 2010).

The Aims of MBT and the Dimensions of Mentalizing

If we refer to the four dimensions of mentalizing described earlier in this chapter, we can see how these theoretical and neurologically based conceptualizations give shape to the practice of the MBT therapist on the ground.

The Automatic–Controlled Dimension. Mentalizing in BPD often tends to be unhelpfully automatic or implicit. It can often be perceived as quite simplistic, nonconscious, nonverbal and unreflective. The processing involved is rapid, requiring little attention or focus. The MBT therapist aims to slow down the patient's thinking, and move them to a more reflective, explicit form of mentalizing that requires more conscious, verbal attention. BPD patients are particularly likely to fall back on this automatic reliance on affective, nonreflective mentalizing at moments of intense emotional arousal (e.g., challenging interpersonal situations, feelings of shame, guilt, anger or inadequacy). Therefore, encouraging the patient to shift toward more reflective controlled form of interpersonal thinking at such moments is a critical challenge for both MBT therapist and patient.

The External–Internal Dimension. Patients with BPD tend to interpret the mental states of others on the basis of exterior cues—physical and visible features such as gestures or actions, or indeed, their own actions. The therapist, then, attempts to move the patient's focus on to mental interiors: the thoughts, feelings, history and experiences that might offer further insight into how someone behaves. This attempt at counterbalancing impression based on appearance with inference involves not only slowing patients down and encouraging them to recognize the assumptions they have made, but also to start to consider the subtleties and complexities of people's subjective experiences.

The Affective–Cognitive Dimension. Patients with BPD often over-rely upon the propositional logic of emotion in assessing subjective states, and indiscriminately apply the very particular logic of emotion to wider thoughts and beliefs. When this emotional logic is extended to cognitions in this way, the patient makes assumptions of psychic equivalence (i.e., "I am thinking this way, and thus this must be the way you are thinking too"). In such a situation, the approach of the MBT therapist would be to help the patient step back from this collapsing of appearance and reality, and draw attention to the patient's vulnerability to excessive and unreasonable certainty on the basis of relatively flimsy cues. The MBT approach works on broaching the disconnection between cognitive and emotional experience. The patient with BPD will frequently experience moments where he or she is overwhelmed by affect; the response of the MBT therapist at such times should be to help the patient integrate this intense sense of affective knowledge or awareness (whether about the self or others) with more reflective and cognitive knowledge. On the other hand, when the patient is functioning in pretend mode, he or she may display apparent cognitive understanding of mental states, but be disconnected from their emotional significance. In both cases the imbalance is indicated by the absence of doubt that cognition about emotion or belief brings to the foreground. For example, a patient might describe an overwhelming feeling of being bad inside, which may, when more carefully represented, become a more specific sadness about failures, which can then helpfully be considered while the patient is experiencing this bad feeling.

The Self–Other Dimension. The limitations of cognitive, reflective modes of understanding give excessive weight to the influence of mental states sensed in others, leaving the individual vulnerable to emotional contagion and suggestibility through others' subjective experience. This temporary disappearance of the self–other boundary is addressed by MBT through the systematic emphasis of the

absent pole of the self–other construct. When a patient starts to talk about his or her own state in a nonmentalizing way, a strategy employed in MBT practice is for the therapist to shift the patient's attention to the mental state of others. Conversely, when the patient becomes intensely concerned with someone else's mental state, the patient should be encouraged to consider how this preoccupation is affecting his or her own functioning. Working to shift the patient's thoughts and feelings between the self and the other in a consistent, flexibly responsive way that counters the patient's preoccupations is a core element of the MBT therapist's practice. It is a process that, critically, requires the therapist to recognize the patient's proneness to psychic equivalence and to consistently seek to create an awareness of the differentiation between the self and others.

Focus of MBT

In working across the four mentalizing dimensions, the basic and consistent aim of MBT is to reestablish mentalizing when it is lost, or rather to work to maintain a balanced form of mentalizing. MBT is not a therapy that claims to seek structural or personality change in the patient with BPD, or to alter their cognitions or schemas. Rather, the emphasis is on improving the patient's capacity for mentalization and to make his or her mentalizing capacities (or skills, to use the frame of dialectical behavior therapy) more stable and robust so that the patient is more able to manage affect and think about problems, particularly within interpersonal relationships. Throughout the treatment, MBT therapists are expected to focus on the patient's subjective sense of self; this requires the therapist to identify and work with the patient's mentalizing capacities at any moment, and to be able represent internal states in themselves and in their patient as these are likely to be experienced by the patient at that moment. To think of this process concretely, therapists do not interpret the patient's state of mind; rather, seeing themselves as sitting side by side with the patient, they endeavor to describe their sense of how the patient is seeing the world and, using this as the platform for further exploration, elaborate this view and its implications, gently presenting alternative perspectives once they feel confident that the patient senses that they can see the world through the patient's eyes.

This careful attention to the BPD patient's current mental state, while activating an attachment relationship through the therapist's presence in the patient's life as a significant (potentially caregiving) figure, serves to enhance the patient's mentalizing capacities, hopefully without generating the iatrogenic effects that can arise from the activation of a disorganized attachment system. To avoid the negative effects so often experienced in conventional psychodynamic treatment of BPD, the MBT approach avoids situations where patients are expected to talk about mental states that they cannot link to subjectively felt reality and instructs the therapist to moderate the affective tone of interventions to maintain a constant distance—not too arousing but arousing enough.

The Inquisitive Stance and Interventions in MBT

The MBT model involves (1) a deemphasis of deep unconscious interpretations in favor of conscious or near-conscious content; (2) a modification of therapeutic aim, especially with severely disturbed patients, from insight to recovery of mentalizing (i.e., achieving representational coherence and integration); (3) careful avoidance of descriptions of complex mental states (e.g., conflict, ambivalence, unconscious) that are incomprehensible to a person whose mentalizing is vulnerable; and (4) avoidance of extensive discussion of past trauma, except in the context of reflecting on current perceptions of the mental states of maltreating figures and changes in mental state from being a victim in the past versus one's experiences now.

To maximize the impact on the patient's ability to think about thoughts and feelings in relationship contexts, especially in the early phases of treatment, the therapist is most helpful when interventions (1) are simple and easy to understand; (2) are affect focused; (3) actively engage the patient; (4) focus on the patient's mind rather than on his or her behavior; (5) relate to a current event or activity, whatever the patient's currently felt mental reality (in working memory); and (6) make use of the therapist's mind as a model (by therapists disclosing their own anticipated reaction in response to the event being discussed, i.e., talking to the patient about how the therapist anticipates that he or she might react in that situation). This requires the therapist to flexibly adjust the complexity and emotional intensity of interventions in response to the intensity of the patient's emotional arousal. As we have noted, the MBT therapist needs to be vigilantly aware of the patient's current mentalizing capacity and how it fluctuates.

Pseudomentalizing and other fillers to replace genuine thought about thought are explicitly identified by the therapist, and the lack of practical success associated with them should be clearly highlighted. Often, the MBT therapist is required to step in to interrupt discourse that is clearly in the pretend mode, which is the most likely stance taken by an individual predisposed to hypermentalizing (Sharp et al., 2011). Only through interrupting pseudomentalizing can patients learn about how they think and feel about themselves and others, how that shapes their responses to

others, and how errors in understanding self and others may lead to inappropriate actions. Put simply, unlike other insight-oriented therapies, in MBT it is not for the therapist to tell patients about how they feel, what they think, how they should behave, or what the underlying reasons may be, conscious or unconscious, for their difficulties. Rather, the therapist uses and models the *inquisitive stance*, an interpersonal stance that fundamentally entails that the therapist does not know the mental states of the patient, but is interested to find out what the patient thinks and feels, and shows openness to being wrong (demonstrating humility) and to be positively surprised by the patient's states of mind.

From a practical standpoint, an effective mentalization-based intervention may unfold along the following lines: (1) the therapist identifies a break in mentalizing (described earlier in this chapter as psychic equivalence, pretend, or teleological modes of thought); (2) the patient and therapist rewind to the moment before the break in subjective continuity; (3) the current emotional context for the break in the session is explored by identifying the momentary affective state between the patient and therapist; (4) the therapist explicitly identifies and claims responsibility for their own contribution to the break in mentalizing; and (5) the therapist seeks to help the patient to understand the mental states implicit in the current state of the patient–therapist relationship at that moment (to mentalize the relationship).

Key to the MBT approach is the therapist's mentalizing stance (or inquisitive stance), which serves to highlight their own interest in how mental states underpin behavior, describing their own understanding and inferences (while acknowledging the opaqueness of mental states), and demonstrating how such information can help the patient to make sense of their experiences. The therapist's mentalizing therapeutic stance should include (1) humility deriving from a sense of not knowing; (2) whenever possible, taking time to identify differences in perspectives; (3) legitimizing and accepting different perspectives; (4) active questioning of the patient in relation to their experience, asking for detailed descriptions of experience ("what" questions) rather than explanations ("why" questions); and (5) eschewing the need to understand what makes no sense (i.e., saying explicitly that something is unclear). An important component of this stance, as noted, is for the therapist to monitor and own up to their own mistakes, to take their share of the responsibility for a temporary failure of communication between therapist and patient. This not only tends to lower arousal, thus increasing the likelihood of adequate mentalizing, but also offers invaluable opportunities to explore how mistakes can arise out of mistaken assumptions about opaque mental states and how misunderstanding can lead to massively aversive experiences.

In this context, it is important to be aware that the therapist is constantly at risk of losing their capacity to mentalize in the face of a nonmentalizing patient. Consequently, we consider therapists' occasional enactments as an acceptable concomitant of the therapeutic alliance, something that simply has to be acknowledged. As with other instances of breaks in mentalizing, such incidents require that the process is rewound and the incident explored. Hence, in this collaborative patient–therapist relationship the two partners have a joint responsibility to understand enactments.

Effectiveness of MBT

The evidence base for the effectiveness of the mentalization-based therapeutic approach for BPD patients has been tested in different randomized control trials (RCTs). In an RCT of MBT for BPD in a partial hospital setting (Bateman & Fonagy, 1999, 2001), significant and enduring changes in mood states and interpersonal functioning were associated with an 18-month program. Outcome measures included frequency of suicide attempts and acts of self-harm, number and duration of inpatient admissions, service utilization, and self-report measures of depression, anxiety, general symptom distress, interpersonal function, and social adjustment. The benefits, relative to treatment as usual (TAU), were large (with a number needed to treat of approximately 2), and were observed to increase during the follow-up period of 18 months. Analysis of participants' healthcare utilization suggested that day hospital treatment for BPD was no more expensive than general psychiatric care and showed considerable cost savings after treatment (Bateman & Fonagy, 2003). A follow-up study of BPD patients 5 years after all treatment was completed and 8 years after initial entry into treatment, comparing patients treated with MBT versus those receiving TAU, has found that those receiving MBT remain better than the TAU group. Superior levels of improvement were shown on levels of suicidality (23% in the MBT group vs. 74% in TAU group), diagnostic status (13% vs. 87%), service use (2 years vs. 3.5 years), and other measurements such as use of medication, global function, and vocational status (Bateman & Fonagy, 2008a).

Two well-controlled single-blind trials of outpatient MBT have been conducted with adults with BPD (Bateman & Fonagy, 2009) and adolescents presenting to clinical services with self-harm, the vast majority of whom met BPD criteria (Rossouw & Fonagy, 2012). In

both trials MBT was found to be superior to TAU in reducing self-harm, including suicidality, and depression. Importantly, in the Bateman and Fonagy trial, the control group received a manualized, highly efficacious treatment, structured clinical management, but MBT was superior, particularly in the long run (Bateman & Fonagy, 2009). Further, improvements generated by MBT in adolescents appear to have been mediated by improved levels of mentalization, reduced attachment avoidance, and assuagement in emergent BPD features: patients in the MBT group showed a recovery rate of 44% compared with 17% in the TAU group (Rossouw & Fonagy, 2012).

Three more recent studies provide further support for MBT in patients with BPD. An RCT from Denmark investigated the efficacy of MBT versus a less intensive, manualized supportive group therapy, both delivered in combination with psychoeducation and medication, in patients diagnosed with BPD (Jorgensen et al., 2013). Patients were randomly allocated to MBT ($n = 58$) or the specialist combined treatment ($n = 27$). Both the combined MBT treatment and the less intensive supportive therapy brought about significant improvements on a range of psychological and interpersonal measures (e.g., general functioning, depression, and social functioning) as well as the number of diagnostic criteria met for BPD; effect sizes were large ($d = 0.5$–2.1). The combined MBT therapy was superior to the less intensive supportive group therapy only on therapist-rated Global Assessment of Functioning. No follow-up or cost-effectiveness data are available from this study. Furthermore, the same therapists conducted both treatments (and thus there was a high risk for spillover effects between the two treatments), and incomplete data was a significant limitation.

A naturalistic study by Bales et al. (2012) in the Netherlands investigated the effectiveness of an 18-month, manualized program of MBT in 45 patients diagnosed with severe BPD. There was a high prevalence of comorbidity of Axis I and Axis II disorders. Results showed significant positive change in symptom distress, social and interpersonal functioning, and personality pathology and functioning; effect sizes were moderate to large ($d = 0.7$–1.7). Also, these authors showed that care consumption (additional treatments and psychiatric inpatient admissions) decreased significantly during and after treatment. The lack of a control group in this study limits the ability to draw conclusions about the efficacy of the MBT intervention. A multisite randomized trial by the same group comparing intensive outpatient and partial hospitalization-based MBT for patients with BPD is currently under way.

Finally, a recent naturalistic trial studied the feasibility and effectiveness of inpatient MBT for adolescents with borderline symptoms in 11 female adolescents aged 14–18 years (Laurenssen et al., 2014). Results showed significant decreases in symptoms and improvements in personality functioning and quality of life 12 months after the start of treatment, with effect sizes between $d = .58$ and 1.46, indicating medium to large effects. Further, 91% of the adolescents showed reliable change on the Brief Symptom Inventory, and 18% moved to the functional range on this measure.

Attachment, Mentalizing, and Epistemic Trust

MBT is not the only effective therapy for BPD, and a key fact associated with the disorder is that numerous coherent approaches to treatment appear to produce significant improvement (Stoffers et al., 2012). At least nine different forms of therapy have been trialed in at least 20 randomized trials with waitlist or TAU comparisons and three large head-to-head comparison studies. Although there is clearly more evidence for dialectical behavior therapy than any other therapy (Kliem, Kroger, & Kosfelder, 2010), its superiority to other methods is not apparent from head-to-head comparison studies (Clarkin, Levy, Lenzenweger, & Kernberg, 2007; McMain et al., 2009) and some effectiveness trials (Feigenbaum et al., 2012). We propose that while the mentalizing approach may be only one of the effective approaches to treatment, the theoretical understanding of BPD outlined in this chapter may provide helpful insights as to why such a wide range of technical approaches appears to produce evident improvements in the condition.

Notwithstanding incommensurate techniques, all the effective treatments seem to be characterized by three features: *consistency*, *coherence*, and *continuity*. The common factor explaining effectiveness could be linked to the constraint of these three Cs. Here, we present a recent extension of the mentalizing approach that may shed more light on putative mechanisms of change in the treatment of BPD patients.

How Do We Learn From Experience?

We now have considerable evidence that the caregiver's capacity to mentalize predicts secure attachment in the child. Studies looking at different ways caregiver mentalizing is operationalized—including prenatal reflective function (Fonagy et al., 1991), child-specific reflective function (Slade, Grienenberger, Bernbach, Levy, & Locker, 2005), mind-related comments (Meins, Fernyhough,

Fradley, & Tuckey, 2001; Meins et al., 2002), and a diverse range of other measures (Aber, Slade, Berger, Bresgi, & Kaplan, 1985; Koren-Karie, Oppenheim, Dolev, Sher, & Etzion-Carasso, 2002; Oppenheim, Koren-Karie, & Sagi, 2001; Solomon & George, 1999)—have found that each of these aspects of mentalizing capacity predicts attachment security in the child. Furthermore, the caregiver's capacity to mentalize can offer protection from risk factors in the caregiver that are associated with generating attachment insecurity, such as the transmission of maternal trauma and disruptive maternal behaviors. We also now know that the benefits of caregiver mentalizing extend beyond attachment outcomes: it is associated with higher performance in children's social cognition tasks (Laranjo, Bernier, Meins, & Carlson, 2010; Meins et al., 2002), as well as general social cognitive development (Meins et al., 2003). By contrast, social environments characterized by adversity in child development (e.g., neglect, abuse) impair the development of cognition (Ayoub et al., 2009; Fernald, Weber, Galasso, & Ratsifandrihamanana, 2011; Goodman et al., 2010; Rieder & Cicchetti, 1989).

The impact of the quality of a caregiver's mentalizing behavior has, then, been extensively analyzed and assessed. The related question is: how does the child learn from their caregiver's behavior? This is an issue that has powerful ramifications for our understanding of human social development, as well as—more pertinently for our purposes here—our understanding of how BPD emerges, and how therapeutic interventions with this disorder might work. We argue elsewhere (Fonagy, Luyten, & Allison, in press), on the basis of pioneering work by Dan Sperber (Sperber et al., 2010; Wilson & Sperber, 2012) and accumulating evidence (e.g., Corriveau et al., 2009), that secure attachment experiences pave the way not only for the acquisition of mentalizing but also potentially more generally for the formation of *epistemic trust* (defined as an individual's willingness to consider communication conveying new knowledge from someone as trustworthy, generalizable and relevant to the self).

Natural Pedagogy and Epistemic Trust

Csibra and Gergely's (2009) theory of natural pedagogy (ToNP) may offer a compelling model to explain the way attachment history could create distinct types of epistemic states. The ToNP posits a human-specific, cue-driven social cognitive adaptation of mutual design dedicated to ensuring the most effective and efficient transfer of culturally relevant knowledge. Csibra and Gergely argue that human communication is the evolutionary product of the requirement to transmit cognitively opaque cultural knowledge: generic knowledge that is robust to interference, is kind-generalizable, and becomes experienced as shared in the sense that it immediately generates an expectation that others belonging to one's social group also possess this knowledge. They use an idea first discussed by Bertrand Russell (1940), but extensively used by Sperber and Wilson (1995), suggesting that certain signals are employed by an agent and prepare the addressee for the intent of the agent to communicate. This communicational cue may also serve the function of counteracting natural epistemic vigilance (the self-protective suspicion toward potentially damaging, deceptive, or inaccurate information). Russell pointed to a process of *ostentiation* (signaling of communicative intent) that takes place as part of communication. *Ostensive cues,* it is claimed by the ToNP model, generate a particular attentional state where natural disbelief is momentarily suspended and the addressee feels that the subsequent communication conveys pieces of knowledge that will contain information specifically relevant to them, which should be remembered and encoded with knowledge generally relevant to social situations involving the self with others. Such information can be about an object, or about the other's views and attitudes about the object—or indeed the beliefs communicated by the other about the self—that is to be regarded as generalizable and relevant across situations. The information can be laid down and used as part of procedural and semantic memory, not uniquely or primarily episodic memory. The distinction between these memory systems is of course well established in neuroscience (Squire, 2004).

In a securely attached child, the caregiver is felt to be a reliable source of knowledge, as the predictors of secure attachment relationships are in essence also ostensive communication cues. The consistent emotional responses of a sensitive caregiver are clearly enacted to the child via the caregiver's ostensive cues, which include eye contact, turn-taking contingent reactivity, and the use of a special tone of voice, all of which appear to trigger a special mode of learning in the infant. The marked nature of mirroring[7] of the infant's emotional expression by the caregiver, which underpins the development of emotion understanding, can be seen as ostensive in nature, signaling the relevance of the caregiver's display to the infant's accumulating knowledge base about their own subjective experience (Fonagy et al., 2007a).

[7]Marked mirroring of the infant by the caregiver refers to the use of exaggerated facial displays and the voice to reflect how the infant is feeling back to the infant, but in a play-acting manner.

The biological predisposition of the caregiver to respond contingently to the infant's (at first automatic) expressive displays creates the foundation for the infant to acquire further knowledge from that individual. During marked mirroring interactions (Fonagy et al., 2002; Gergely & Watson, 1996), the attachment figure will mark his or her referential emotion displays in a manifestative manner to signal the generalizability of knowledge and effectively instruct the infant about the infant's subjective experience: "look at me" (marked display/ostensive cue), "this is what you are feeling" (culturally transmitted self-knowledge) (Fonagy, Gergely, & Target, 2007b). In other words, marking by the caregiver, which is part of good enough mirroring, serves as an ostensive cue to the infant that the concurrent mirrored affect signals are relevant and generalizable. Human infants display a species-specific sensitivity in relation to certain nonverbal ostensive behavioral signals (Csibra & Gergely, 2006, 2009, 2011). They attend preferentially to such signals and the impact of these signals on their behavior is readily apparent.

In brief, ostensive cues trigger epistemic trust and simultaneously engender secure parent–child attachment (Fonagy et al., 2007b). They set aside the biological protection provided by epistemic vigilance. They open a channel of information exchange designed by evolution to transmit and assist in receiving knowledge about the social and personally relevant world, going beyond the specific experience, all the while remembering the information and encoding it with the authority but not the person of the communicator. Ostensive cues signal that we must go beyond the specific physical experience and acquire information that is relevant across a range of settings. Epistemic trust is there to ensure that we can safely change our position, and it triggers the opening of an evolutionarily protected *epistemic superhighway* that signals readiness for knowledge acquisition.

There are several fascinating developmental experiments summarized by Csibra and Gergely (2009), which give powerful support to the ToNP. They offer compelling evidence from infancy for the power of this dialogic learning process. In one simple demonstration, 6-month-old infants were shown to follow an agent's gaze shift selectively to an object only if it had been preceded either by eye contact with the infant or by infant-directed speech (Senju & Csibra, 2008). Shared attention with an agent is triggered by the infant experiencing the agent's interest. The interest triggers the infant's expectation (epistemic trust) that there may be something relevant for the infant to learn.

A second study employing an automated eye-tracker used an infant-induced contingent reactivity paradigm (Deligianni, Senju, Gergely, & Csibra, 2011). During the familiarization phase, 8-month-old infants observed a display where five unfamiliar animated objects (looking more like jugs or kettles than anything else) were displayed. Four of these, in the four corners of the display, moved unpredictably. The object at the center acted differently in two conditions. In the interactive condition, whenever the infant's gaze wandered toward the object, it would respond to the infant's gaze with movements and sound. In the control condition, the central object would move a comparable amount but this would be independent of the infant's gaze. In the test phase, only three objects were present. The central object in this phase turned toward either the left or the right object. It should be noted that although none of the five jug-like objects had eyes, they had a clear, unequivocal front signaled by a pointed "hat" and an elongated "nose" (somewhat reminiscent of a kettle with an upturned beak). The 8-month-olds in the interactive condition detected the contingent activity of the central object and looked at the object it turned toward (i.e., followed its "gaze") far more. In the noncontingent control condition, the infants did not look for longer, more frequently, or more promptly at the object that the central object turned toward. It seems that the contingent reactivity of this nonhuman and somewhat bizarre object was sufficient to influence the infant's orientation. The study is important in showing that it is the experience of response-induced contingencies that creates epistemic trust and elicits a joint attention response.

From all that we know about the nature of attachment, it is evident that secure attachment is driven by sensitive responsivity contingent upon an infant's reaction (Belsky & Fearon, 2008; Marvin & Britner, 2008). In other words, secure attachment is created by a system that is capable of simultaneously generating a sense of epistemic trust. In a longitudinal study of attachment, 147 children assessed for attachment in infancy were tested twice for epistemic trust at the ages of 50 and 61 months (Corriveau et al., 2009). In this study, the child's mother and a stranger made conflicting claims to a child concerning (1) the name of a novel object; (2) the name of a hybrid animal made up of 50% of each of two animals (e.g., an image made up of 50% rabbit and 50% squirrel; the mother might call it a squirrel, while the stranger says it is a rabbit); and (3) the name of a hybrid animal made up of 75% of one animal and 25% of another. In the last case it was always the mother who made the improbable claim (e.g., that a picture made up of 75% bird and 25% fish was a fish), while the stranger gave the more likely answer (in this example, bird). The simple question was who the child

would spontaneously turn to for information and believe, and whether this behavior was moderated by the history of attachment security. The nature of a child's attachment relationship turned out powerfully to condition the child's trust in the information imparted by the attachment figure (mother) and others (strangers) as informants. Children who were securely attached in infancy displayed a flexible strategy, showing a preference toward accepting claims made by their mother when appropriate. Insecure-avoidant children appeared to withhold trust in their mother, preferring to attend to information from the stranger, while insecure-resistant children withheld trust in the stranger even when their mother made improbable claims. Children with insecure-disorganized histories evidenced what we may call *epistemic hypervigilance*; they appeared to regard both sources of information with suspicion.

Security of attachment, rooted in a history of feeling recognized, appears to increase the likelihood of trust in the source of communication when it is reasonably credible. Yet a secure attachment history also generates confidence in one's own experience and belief and empowers one's (i.e., the child's) judgment. A history of attachment avoidance may generate epistemic mistrust, while anxious attachment creates epistemic uncertainty through overreliance on the views of the attachment figure. Disorganized attachment, rooted in a history of chronic misattunement, unsurprisingly can create mistrust of both the attachment figure and strangers as a source of information. It is the unresolvable question of "whom can I trust?" that might contribute to epistemic hypervigilance in a child with a history of disorganized attachment. The child with a history of attachment disorganization mistrusts information from both attachment figures and strangers, and even mistrusts their own experience. While an insecure attachment history may preclude complete confidence in one's subjective experience, an organized strategy biases either toward or away from the attachment figure. But if neither can be trusted an interminable epistemic search may ensue, associated with disorganized attachment. The child seeks others to confirm or deny his or her own understanding, which he or she has little faith in, but, not being able to trust the information received from others, is left in a state of continued uncertainty. Ultimately, this generates a state of interminable searching for the validation of experience, coupled with the chronic lack of trust that we have termed epistemic hypervigilance.

We suggest that while attachment may be a key mechanism for the mediation of epistemic trust, it is secondary to an underlying biological process preserved by evolution. We have seen that stimuli such as the bizarre kettle-shaped object in the study described previously are capable of at least momentarily triggering the same category of response as human beings. In other words, secure attachment is not likely to be a *necessary* condition for generating epistemic trust but it may be *sufficient*, and the most *pervasive* in early childhood because it is a highly evolutionarily effective indicator of trustworthiness. Given that the human infant needs to overcome the self-preservative barrier created by natural epistemic vigilance and open their mind to acquiring the millions of bits of culturally relevant information on which their survival will ultimately depend, it would have been foolhardy for nature (evolution) not to gift us with a mechanism of deferential knowledge transmission that would create a kind of epistemic superhighway between learner and teacher, based normally on a shared genetic inheritance (Hamilton, 1964).

Attachment, Mentalizing, and Epistemic Trust

Looked at from a distance, micro-analytic (e.g., Beebe et al., 2010) and more global (e.g., DeWolf & van IJzendoorn, 1997; Isabella, Belsky, & von Eye, 1989; Kiser, Bates, Maslin, & Bayles, 1986; Mills-Koonce et al., 2007) ratings of sensitive caregiving can be seen as in essence recognizing the child's agentive self. It is this recognition that we believe offers the cognitive advantage to secure attachment, which has been fairly consistently noted, although not, to our knowledge, commonly studied (e.g., Crandell & Hobson, 1999; Jacobsen & Hofmann, 1997; Moss, Rousseau, Parent, St.-Laurent, & Saintong, 1998) and contributes to the cognitive disadvantage of developmental adversity we considered above (Ayoub et al., 2009; Fernald et al., 2011; Goodman et al., 2010; Rieder & Cicchetti, 1989). We believe that attachment establishes, through the down-regulation of affect triggered by proximity-seeking in the distressed infant, not only a lasting bond; it also opens a channel for information to be used for the transfer of knowledge between the generations.

Attachment insecurity is likely to be associated with a greater likelihood of cognitive closure, a lower tolerance for ambiguity, and a more pronounced tendency for dogmatic thinking (Mikulincer, 1997). Saving intellectual effort and adopting stereotypes is also more likely in individuals whose attachment is insecure (Mikulincer, 1997). The same predisposition to knowledge inflexibility is revealed by the tendency of insecure individuals to make judgments on the basis of early information and to pay insufficient heed to subsequent data even if it is incompatible with the configuration first created (Green-Hennessy & Reis, 1998; Mikulincer, 1997). Insecure individuals, who fear the loss of attachment figures, also anxiously hold on to their initial

constructions. Kruglanski (Kruglanski, 1989; Kruglanski & Webster, 1996; Pierro & Kruglanski, 2008) proposed the concept of *epistemic freezing*, characterized by a tendency to defend existing knowledge structures, even when they are incorrect or misleading (see also Fiske & Taylor, 1991). Returning to the earlier theme of seeing adversity as a cause not of deficit but rather of superior adaptation to challenging environments (Frankenhuis et al., 2013), we may see such a defensive strategy as adaptive if an individual's self-esteem is vulnerable. Cognitive closure, dogmatism, and conservatism may simply be strategies to create a bulwark to safeguard an inadequately individuated self (Bowlby, 1980). By contrast, the greater confidence of secure individuals that they will be able to recover from dysregulation also enables them to be less defensive in relation to opening their minds to information that may challenge their assumptions.

Mikulincer (1997) suggested that insecure individuals were more readily threatened by information that challenged their knowledge structures because of the vulnerability of their sense of self, and vulnerability in particular to being emotionally overwhelmed. If emotional dysregulation is experienced as a real and imminent threat, they may opt for knowledge stability, as it temporarily serves to down-regulate arousal. Such individuals are less likely to revise their knowledge in the face of information that challenges their assumptions (Green-Hennessy & Reis, 1998; Green & Campbell, 2000; Mikulincer, 1997; Mikulincer & Arad, 1999), as if they not only had less confidence in the robustness of their bond to their attachment figure, but also feared the loss of epistemic trust. In sum, we assume that the epistemic superhighway provided to us by evolution for us to learn from experience is partially closed to those whose attachment to their caregiver is insecure.

Vulnerability for BPD is associated with conditions in which there is a marked absence of respect for the recipient of communications as an active agent. To summarize, (1) as we have shown already, insecure attachment is associated with BPD; (2) insecure and frequently mindless, abusive child–caregiver interactions antedate BPD (e.g., Pietrek et al., 2013); and, perhaps most pertinent, (3) anomalies of early caregiver–infant communication predict not only attachment disorganization but, in some carefully conducted longitudinal studies (e.g., Lyons-Ruth, Bureau, Holmes, Easterbrooks, & Brooks, 2013), the likely emergence of personality pathology.

Detailed inquiry into these high-risk anomalies of parent–infant communication could be seen as part of caregiving interactions that may involve the misuse of ostensive cueing. By *misuse of ostensive cueing* we mean using cues to lead the infant to anticipate personally relevant, generalizable knowledge through a kind of pseudosensitivity followed by the transmission of disruptive and even destructive knowledge. Careful examination of the manual for the coding system Disconnected and Extremely Insensitive Parenting[8] (Out et al., 2009; predicting disorganized attachment) reveals a multitude of examples of this pattern. Some of these are: anomalous movements and postures; simultaneous contradictions in vocalizations; suddenly stilling and freezing the posture, or startling in response to the child's behavior; sudden voice alterations; sudden and inexplicable shifts of mood; and fear in relation to aspects of the environment that have no intrinsically frightening aspect. Future research will need to establish whether such anomalous or misused ostensive cues on the part of caregivers, in the context of imparting mirroring information about the child's experience, are particularly associated with the emergence of BPD.

The special significance of emotional neglect and abuse to BPD (as discussed earlier in this chapter) also fits well with ideas linking this disorder to chronic epistemic mistrust. We feel that it is less likely to be the frank brutality of abuse that undermines epistemic trust (although of course it can do) and that neglect and emotional abuse will play a larger role. Taking the perspective of epistemic trust as the mediator of culture and its key underlying engine for progression, we have to see the destruction of trust in social knowledge as a key mechanism in pathological personality development.

Developmental adversity, perhaps most deeply attachment trauma (Allen, 2012, 2013), may trigger a profound destruction of trust. There may be other reasons, but, once lost, the absence of epistemic trust generates an apparent rigidity. The rigidity is in the eyes of the communicator, who, in accordance with the principles of theoretical rationality, expects the recipient to modify their behavior on the basis of the information they have received and apparently understood. But, in the absence of trust, the capacity for change is absent. The information presented is not used to update the individual's social understanding.

[8]The DIP coding system assesses disconnected and extremely insensitive parental behavior. Items from Main and Hesse's (1998) coding instrument, titled "Frightening, Frightened, Dissociated, Sexualized and Disorganized Parental Behavior: A Coding System for Parent–Infant Interactions" are included, as well as items from the system by Bronfman, Parsons, and Lyons-Ruth (1999), titled "Atypical Maternal Behavior Instrument for Assessment and Classification (AMBIANCE)."

In terms of the ToNP (Csibra & Gergely, 2009) the person has (temporarily) lost the capacity for learning. From a therapist's standpoint, he or she has become hard to reach and interpersonally inaccessible.

Implications for the Conceptualization and Treatment of BPD

An individual in a state of epistemic mistrust (or, at an extreme, epistemic petrification) cannot change. A basic route for acquiring culturally relevant knowledge is functioning in only a limited way. The individual cannot change because they cannot accept that the information they receive is relevant to them or usefully generalizable to other social contexts. It is received episodically and remembered within autobiographical recall as simply something that happened, but it is not incorporated into the procedural and semantic systems that govern an individual's behavior across social situations as an element of their participation in the great evolutionary process of transgenerational cultural transmission.

To put it bluntly, we are suggesting that BPD is not a disorder of personality except by some old definitions whereby the term *personality* was used synonymously with *slow-changing*. In fact, BPD (and most, if not all, PDs) describes a state of social inaccessibility. It can be conceived of as a temporary state of incompatibility with a grand evolutionary design of intracultural communication in which we all play a part. It describes a state of isolation from communication from one's partner, one's therapist, one's teacher—all generated by intense and chronic epistemic mistrust.

At its simplest, epistemic mistrust is *not believing what one is told*. To put it more accurately, the person may avow a belief but beyond that is unable to use new information to alter existing schemata of procedural or semantic knowledge in relation to the world as it concerns the self or the other. Epistemic mistrust can be the consequence of high levels of epistemic vigilance (Sperber et al., 2010). It may arise from overinterpretation of the communicator's motives, rather than a more obvious closure to the communicator. For example, we know that emergent BPD is associated with hypermentalization (Sharp et al., 2011, 2013). If the recipient of a communication assumes that the communicator's intentions in communicating are other than those declared, the communication and the communicator's belief will not be treated deferentially and will not be used to update the reservoir of culturally transmitted knowledge. The communication may therefore affect behavior in relation to that particular individual but will not generalize across settings. The recipient of the communication appears to the communicator to be *rigid*.

Of course, the misattribution of intent and treating someone's communicative intent as fundamentally malevolent is part of a schizotypal and paranoid stance that is commonly comorbid with other PD diagnoses (e.g., Pulay et al., 2009; Watson & Sinha, 1998). In some individuals, perhaps for reasons of biological predisposition to hypermentalizing or adverse learning experiences, or both, the primary avenue for modifying stable beliefs about the world has been closed, causing significant disruptions particularly in social situations requiring flexibility and a capacity for learning (e.g., vocational functioning; McGurk et al., 2013). Attachment insecurity antedated by less contingent responsiveness on the part of the attachment figure perhaps leaves behind it a more limited eagerness to modify existing knowledge structures. According to the attachment–epistemic trust hypothesis as outlined above, attachment categories can be conceptualized as manifestations of how a child attributes trust toward possible informers.

Building on the ToNP, BPD could be seen as a consequence of a catastrophic breakdown of epistemic trust, a consequence of a series of failures of communication. By way of either adversity (neglect and abuse), a genetic predisposition to hypermentalize, or a combination of the two, a fundamental lack of trust in communication has built up, which has left the individual with severe mentalizing impairments; at moments of interpersonal pressure they cannot reliably relate to other people's minds as safe, predictable, or even imaginable, and they cannot, at such moments of intense affect, regulate or interpret their own thoughts or emotional processes. It is this epistemic hypervigilance that works to give BPD its qualities of rigidity, or being hard to reach, and storminess of affect. It is, therefore, unsurprising that in the context of such failures of communication, the subjective experience of BPD involves such intensely painful isolation. These difficulties in communication can also generate intense feelings of frustration on the part of therapists seeking to work with patients with BPD. It is now to the question of how therapy can serve to reach patients with BPD that we will turn.

Mechanisms of Change in BPD

As we have seen, a number of therapies appear to be effective for BPD. In other words, for treatments to work, they require a clear theoretical frame and a coherent, well-defined model of reliably delivered treatment. But

beyond this, a wide variety of therapeutic models can (and does) claim to be efficacious. Enumerating generic factors common to such therapies, such as positive regard or validation—which could equally characterize less effective generic supportive techniques—will by itself provide neither an adequate treatment nor an adequate explanation of what makes therapies work. There is a call for a single model of treatment mechanism that is able to accommodate the need for specificity and at the same time offer a parsimonious model explaining the working of the wide range of therapies that are effective in facilitating recovery from this condition. On the basis of the preceding section, we argue that three sets of processes, which we will label *communication systems*, underpin the mechanism of change in BPD. Here we will briefly discuss their nature and how these three systems relate to each other cumulatively to make change possible.

Communication System 1: The Teaching and Learning of Content

As noted, all evidence-based treatments of BPD provide a coherent, consistent, and continuous framework enabling the patient to examine, in a safe and low-arousal context, the issues that are deemed to be central according to the particular theoretical approach (e.g., early schemas, invalidating experiences, object relations, and current attachment experiences). All evidence-based psychotherapies provide skills or knowledge that assist the patient, whether this is part of acquiring strategies to deal with emotional dysregulation or restructuring interpersonal relationship schemata from the past or in the present as part of imparting such content. All evidence-based therapies deliver to the patient a model of mind, of disorder, and a hypothetical process of change that are convincing and accurate enough to enable the patient to feel recognized as an agent. The model contains sufficient information of personal relevance for the patient to experience feeling markedly mirrored or understood. These implicit or explicit explanations are, in essence, ostensive cues; they signal to the patient the relevance of the information that is conveyed by triggering personal recognition in the patient. This process is important because it leads the patient to reduce his or her epistemic hypervigilance as he or she increasingly sees the model's relevance to his or her own state of mind. Thus, acquiring new skills which had been lacking and new (useful) information about oneself has a nonspecific effect of creating openness that eases the learning of the specific content conveyed within the model. Feeling the truth of evidence-based content creates a virtuous cycle, increasing epistemic openness, which in turn allows the patient to take in further information that naturally also serves to reassure and validate. This process of teaching and learning between therapist and patient—of showing the relevance of the wisdom, or model—is facilitated by the experience of feeling mentalized by the felt truth of the content being communicated. The fact that there are so many different therapies, using so many different theoretical models that have been found to have some beneficial effect, indicates that the significance of communication system 1 lies perhaps not in the essential truth of the wisdom of the specific approach, to which the patient is increasingly open in the course of their treatment, but in the fact that it causes the patient to give some weight to a piece of communication from the social world—which brings us to system 2.

Communication System 2: The Re-Emergence of Social Learning

Where communication system 1 concerns the content of *what* is learned in treatment, communication system 2 is concerned with the process of *how* this learning became possible. In the process of effectively passing on knowledge, the therapist creates ways of recognizing the agentiveness of the person, which serve as ostensive cues and convey that he or she is seeking to understand the patient's perspective, which in turn enables the patient to hear and to listen. In effect, the therapist is modeling how he or she engages in mentalizing in relation to the patient. By creating an open and trustworthy social situation, a better understanding of the beliefs, wishes, and desires underpinning the actions of others and of the self is made possible. This in turn allows for a more trusting, less paranoid interpersonal relationship in the consulting room. Ideally, the patient's feeling of having been sensitively responded to opens a second virtuous cycle in interpersonal communication in which mentalizing is regenerated.

The mentalizing of patients, that is, acting in accordance with the patient's perspective, may be a common factor across psychotherapies not because patients need to learn about their minds or to learn about those of others. Rather, mentalizing may be a generic way of establishing increased levels of epistemic trust and therefore achieving change in mental function. The patients' capacity to mentalize improves, we would maintain, in all therapies. This will increase self-control, reduce the experience of mental pain, and improve the ability to think in the content of intense attachment relationships. This has been a key part of our understanding of the mechanisms of change since

the inception of the MBT model (Fonagy & Bateman, 2006b). The patient's subjectivity being understood is vital to this process. It is also vital to a further function of therapy, which we wish to recognize separately, namely: the reopening up of his or her wish to learn about the world, including the social world.

Communication System 3: Learning Beyond Therapy

We hypothesize that feeling understood opens a key biological route to information transmission and the possibility of taking in knowledge that is felt to be personally relevant and generalizable; this is what brings about change in previously rigidly held beliefs. In essence, the experience of feeling thought about enables us to learn new things about our social world.

The therapeutic situation teaches about sources of knowledge. It provides a clear social illustration of trust, making the therapist a *deferential* (Wilson & Sperber, 2012) source of knowledge with the capacity to undo previously rigidly held beliefs about the self, about others, and to dissolve the patient's experience of epistemic isolation, which is embodied in the rigidity of their subjective experience. A third virtuous cycle is initiated. Improved understanding of social situations through improved mentalizing leads to better understanding of important others in the patient's life, which in turn creates the potential for a person to notice a sensitive response and feel understood. Reopening the potential to feel sensitively responded to may in itself initiate more trusting (less paranoid) interpersonal relationships, and thus open the patient up to new understandings of specific social situations as they arise.

We posit that, as the patient's state of epistemic hypervigilance relaxes, his or her capacity for trust increases and he or she discovers new ways of learning about others. This brings with it an increase in the patient's willingness to modify cognitive structures for interpreting the behavior of others. Social experiences that may have been positive, but were in the past discounted as a result of the patient's hypervigilance, now have the potential to have a positive impact. This is the third communication system, which is now available after communication system 2 opened the way to change through enhanced mentalizing. As patients experience social interactions in a more benign way and see the social situation they are in more accurately (e.g., not seeing an experience of temporary social disappointment as an outright rejection), they update their knowledge of both themselves and others.

It is the recovery of the capacity for social information exchange that is at the heart of psychotherapies. They impart an ability to modify or benefit from benign social intentions, and to update knowledge about the self and others in social situations. The improved sense of epistemic trust enables learning from social experience; in this way the third virtuous cycle is maintained beyond therapy.

As therapists we often assume that the process in the consulting room is the primary driver of change. Yet our experience tells us that change is also brought about by what happens beyond therapy, by how a person uses their social environment. Empirical evidence from session-by-session monitoring of change suggests that the therapeutic alliance in the previous session foretells change in the next (Falkenstrom, Granstrom, & Holmqvist, 2013; Tasca & Lampard, 2012). This suggests that change occurs in between sessions but as a consequence of changed attitudes to learning engendered by the therapy. The implication is that the extent of benefit a patient derives from treatment may depend on what is accessible to the patient in his or her particular social world. We predict that psychotherapy for BPD is much more likely to succeed if the individual's social environment at the time of treatment is, by and large, benign.

This admittedly speculative model offers a way of integrating the specific and nonspecific factors in psychotherapy. Specific factors associated with therapies that work create experiences of truth, which in turn encourage a person to learn more. In this process, via a nonspecific channel, the patient's capacity to mentalize is fostered. Both these systems would be expected to lead to symptomatic improvement. Improved mentalizing as well as reduced symptomatology improves the experience of social relationships. It is likely that these new experiences, rather than just what happens in therapy, serve to erode the epistemic hypervigilance that has prevented benign social interactions from changing an individual's experience of themselves and of the social world.

CONCLUSIONS

This chapter has provided a review of the most current thinking within the mentalizing model of the development and treatment of BPD. It is a psychodynamic developmental psychopathology model, which incorporates the latest research findings that have implications for our more complete understanding of BPD at different levels, ranging from psychological to sociocultural and biological/genetic factors. Moreover, we have adopted a life-span approach to BPD; in particular, we have attempted to place a greater emphasis on adolescence and BPD, in keeping with our developmental approach, and our interest in the emergence

of BPD traits as the individual develops and bumps in different ways against their emotional, socioeconomic and genetic environments.

Mentalizing theory initially developed—and has continued to evolve—in the context of clinical practice. This intimacy between theoretical understanding of the phenomenology of BPD and treatment principles runs throughout our thinking on mentalizing, and across the chapter we have sought to explain the latest elaborations of mentalizing theory in conjunction with the empirical research that has shaped and underpins it, and then to describe how these theoretical iterations inform the practice and stance adopted by MBT therapists. We have also further developed the idea of mentalizing, via the concept of epistemic trust, to make a more general proposition about what might make therapeutic interventions for BPD work. In keeping with our conviction that the greatest rigor in both theory and practice is achieved when these two lines run in tight parallel, this proposition serves both a theoretical and a clinical purpose. We have sought to make a theoretical contribution to thinking on how an understanding of, and deficiencies of understanding in, interpersonal relations may be transmitted from caregiver to infant. But also, more pragmatically, we have sought to untangle what processes are shared by more successful evidence-based practices. Mentalizing, we argue, remains a taut and steady thread through the chaos of the multiple therapeutic interventions that currently exist.

As our knowledge derived from the various areas in developmental psychopathology increases the mentalizing model will no doubt continue to develop, leading to a better understanding of BPD and, we hope, to the development of more effective intervention strategies.

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CHAPTER 18

Alcohol Use and the Alcohol Use Disorders Over the Life Course: A Cross-Level Developmental Review

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INTRODUCTION

Alcohol is the world's most common drug of use and abuse. In the form of wine and champagne, it is the drug with which we mark occasions of special joy; in the form of beer, it is the drug of our leisure time activity, and in the United States, in the form of spirits, it is the drug with which we celebrate the transition to adulthood. It is the drug of power and social bonding, and the drug of courtship, and it is also the drug we use to celebrate and remember the death of those close to us. At the same time, when alcohol is used heavily, it contributes to both spousal and nonfamilial violence, child abuse, downward social mobility, unprotected sex, both fatal and nonfatal traffic accidents, fetal alcohol syndrome, and a host of other negative outcomes. Of all the drugs of abuse, it has been rated as the most harmful when considering the joint criteria of harm to others and harm to self (Figure 18.1; Nutt, King, & Phillips, 2010). In short, even in the damage it does, it is closely tied to the fabric of society.

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[1]Color versions of Figures 18.1, 18.2, 18.10 and 18.12 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

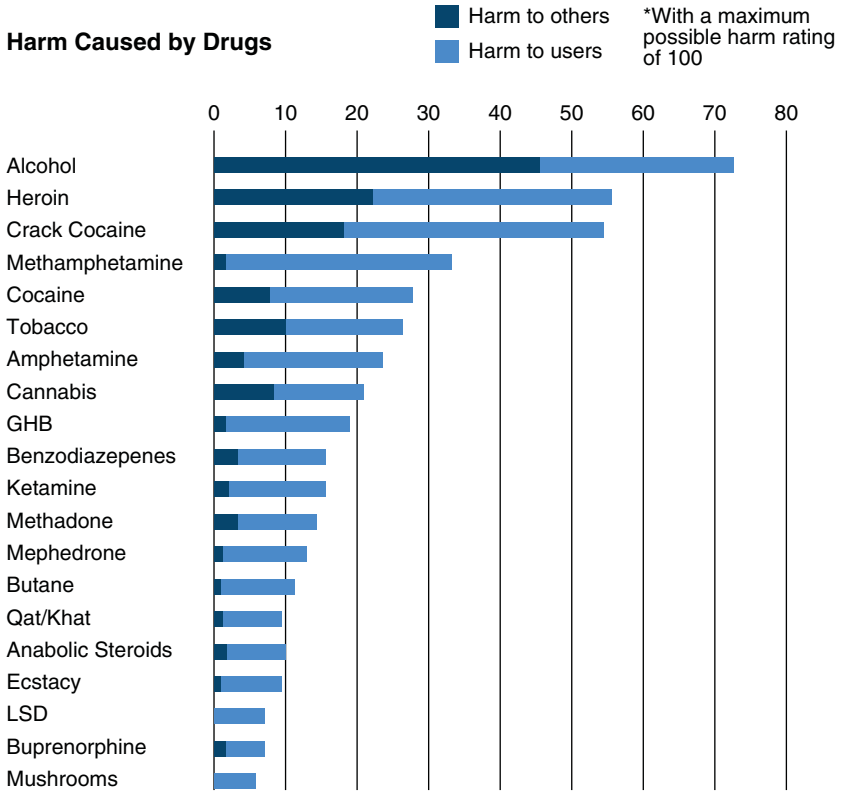


Figure 18.1 Harm caused by drugs. See footnote 1. *Source:* Data from D. Nutt, L. King, & L. Phillips on behalf of the Independent Scientific Committee on Drugs, Drug harms in the UK: A multicriteria decision analysis, *Lancet*, 376, 1558–1565, 2010.

Repeated adverse consequences to self and others that are associated with heavy and compulsive use, that continue despite their obvious personal cost, move the behavior into a different category of experience. Although this behavior is extraordinarily damaging, it does not meet the formal criteria for addiction. The latter involves behavior that is compulsive (i.e., it is experienced as outside the individual's conscious control), and we need to turn to models focused on the genetics and neurophysiology of the behavior to understand the underlying mechanisms driving the process. However, both of these syndromes meet the formal criteria for *DSM-5* alcohol use disorder (American Psychiatric Association, 2013). This issue of heterogeneity of disorder, involves multiple levels of system all the way from the societal to the molecular to be accurately characterized and along the way requires examining relationships across levels of analysis. Because of this complexity the science has tended to be fractionated, and within-level scientific explanations have often been staked out as claims that their domain of explanation encompasses the core elements of the disorder, even though this advocacy tends to be poorly informed about process at other levels of analysis. Although there is no way this chapter can address all of this complexity in great depth, it is driven by the principle that single level explanations are inadequate because they ignore multiple sources of information indicating that the processes are multilevel. The current state of scientific work is sufficiently advanced for us to provide brief summaries of work at most of these levels. Our approach is developmental, in a field where there is still considerable unevenness in recognition of the importance of a life course perspective. In the sections that follow we summarize recent changes in the diagnostic criteria for AUD and briefly summarize the epidemiology of use and disorder, provide a conceptual framework for the matrix of elements needed to specify the mechanistic structure for risk/disorder, briefly summarize earlier efforts to characterize the full matrix, and then provide a heuristic model that will handle the interplay of genes, brain, behavior, context, and development. We then provide two sections on variation in risk and course of disorder. We approach this developmentally. First we review alcohol nonspecific risks (i.e., risks that lead to alcohol use and abuse/disorder but do not pertain to alcohol and as well are risk for behaviors that are not alcohol related, such as

antisocial behavior, depression). We then discuss the development and course of alcohol-specific risk. Following, we review the neurobiological literature on risk development, including the genetics of use, abuse and disorder, as well as recent work on gene–environment (GxE) relationships. This is followed by a section that describes the brain systems and structures involved in creating risk for alcohol problems and disorder; also included is a brief discussion of the role of environment and genetics in the development of neural risk. The final section of the chapter describes some major next-step challenges for the field to address.

EPIDEMIOLOGY

Redefining the Alcohol Use Disorder Diagnostic Criteria

In 1980, with the advent of the third edition of the *Diagnostic and Statistical Manual*, the persistent and damaging problems of alcohol use and abuse were no longer classified as alcoholism. The term alcohol use disorder (AUD)—encompassing both abuse and dependence—was substituted, as more descriptive, precise, and differentiating of the clinical syndrome. In 2013, after using this two stage categorization system for three editions of the DSM, with the advent of the fifth edition of the *Diagnostic and Statistical Manual*, the criterion set for AUD was changed again in a major way. The revision involved collapsing the former abuse and dependence categorizations into a single substance use disorder diagnosis which for alcohol symptomatology meant that there would be only one AUD diagnosis. In the earlier system, alcohol dependence was meant to capture physiological dependence on alcohol and related behaviors, that is, experiencing tolerance and withdrawal symptoms as well as a compulsive need to consume alcohol despite physical and mental health problems and interference in meeting major life responsibilities (e.g., family, work). Alcohol abuse was meant to index less severe drinking problems that increased risk for harm (e.g., drunk driving) or led to problems in social functioning (e.g., lost friends or job due to drinking), but not physiological dependence. The conceptual framework was that abuse was an early manifestation of the disorder that could progress to its more severe and addictive form, dependence, but not necessarily.

There were several problems with this conception. One was that there was not a clear distinction in severity, so that some abuse symptoms were less prevalent and/or more severe than some dependence symptoms. In addition, item response theory models supported a dimensional or continuum model of alcohol use problems covering abuse and dependence, and total number of symptoms—rather than whether symptoms were abuse or dependence—was the best predictor of disability indicators (Borges et al., 2010; Saha, Chou, & Grant, 2006). Also, abuse was not a clear prodromal condition for dependence; that is, many people meant criteria for dependence without having abuse (Hasin & Grant, 2004). Another issue was that only one symptom was necessary for abuse, such as hazardous use. Legal problems due to drinking—such as drunk driving only once—would meet this criterion, yet of themselves these behaviors were not sufficient to be regarded as disorder. Inclusion of criteria such as this ended up yielding extremely high lifetime prevalence rates. There were also problems with the alcohol dependence specifiers, which sometimes resulted in diagnostic orphans, that is, people with two symptoms of dependence but none of abuse, who would not qualify for any diagnosis. The revised diagnostic criterion set is an attempt to simplify this system by combining the abuse and dependence categories, and utilize mild, moderate, and severe specifiers for severity. Last, a new symptom that assesses craving was added. Though there was much debate as to the incremental contribution of adding an addiction symptom, there was sufficient consensus of its utility for enough drugs of abuse (although not necessarily alcohol) to incorporate it as one of the substance use disorder criteria.

Epidemiologic Data

Since epidemiological data on the new *DSM-5* criterion set are not yet available, we discuss findings using the *DSM-IV* criteria for alcohol abuse and dependence. Table 18.1 provides the 12-month and lifetime prevalence rates (percentages) for *DSM-IV* alcohol abuse and dependence, based on the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Hasin, Stinson, Ogburn, & Grant, 2007). NESARC was conducted in 2001–2002 and included 43,093 respondents age 18 to over 65. To give a broader perspective on the alcohol problem, we also present rates for illicit drug abuse and dependence (Compton, Thomas, Stinson, & Grant, 2007). A number of points about these prevalence rates are of importance.

1. Alcohol abuse and dependence are the most common of the substance use disorders.
2. Among men, 4 in 10 adults have at some point in their lives met either abuse or dependence criteria.
3. Gender differences are significant, and are of the order of 2:1 for abuse, and 2.5:1 for dependence.

TABLE 18.1 Lifetime and 12-Month Prevalence of *DSM-IV* Substance Use Disorders

Disorder	Total lifetime	12 month	Male lifetime	12 month	Female lifetime	12 month
Alcohol abuse without dependence	17.8	4.7	24.6	6.9	11.5	2.6
Alcohol dependence	12.5	3.8	17.4	5.4	8.0	2.3
Alcohol abuse/ dependence combined	30.3	8.5	42.0	12.4	19.5	4.9
Other drug abuse without dependence	7.7	1.4	10/6	2.0	0.4	
Other drug dependence	2.6	0.6	3.3	0.9	2.0	0.4
Other drug abuse/ dependence combined	10.3	2.0	13.8	2.8	7.1	1.2

National Epidemiological Survey on Alcohol and Related Conditions data, weighted noninstitutionalized U.S. population percentage estimates from persons 18 years or older.

Sources: Data from D. S. Hasin, F. S. Stinson, E. Ogburn, & B. F. Grant, Prevalence, correlates, disability, and comorbidity of comorbidity of *DSM-IV* alcohol abuse and dependence in the United States, *Archives of General Psychiatry, 64*, 830–842, 2007, and from W. M. Compton, Y. F. Thomas, F. S. Stinson, & B. F. Grant, Prevalence, correlates, disability, and comorbidity of *DSM-IV* drug abuse and dependence in the United States: Results from the national epidemiologic survey on alcohol and related conditions, *Archives of General Psychiatry, 64*, 566–576, 2007.

4. Abuse without dependence represents over 50 percent of the life course problem, and the current (12 month prevalence) problem. Or, to put these figures in a slightly different perspective, over 50 percent of the lifetime national problem is of subclinical proportions, but involves socially and personally significant misbehavior (e.g., compromised driving, risky sex, date rape, job absenteeism, neglect of household responsibilities).
5. Other drug disorders are substantially less of an issue than alcohol use disorders, with a ratio of 12-month alcohol to drug use disorder of over 4:1 (Figure 18.1).
6. Other drug disorders are to a large degree superimposed upon alcohol use disorders, given that only a small minority of 12-month drug use disorders occur without a concomitant alcohol diagnosis.
7. The greater visibility of other drug disorders is likely because the disorders are more dramatic, hence socially compelling, because they appear to be more of a threat to the social order (e.g., because of their links with crime, as well as out of the belief that they may be less responsive to treatment), and because the social costs involved in interdiction and treatment are proportionately much larger. The lay view, as well, is that the disorders occur in isolation, which heightens the differentiation between the different types of drug involvement.

As already noted but not shown in the table, AUD is the nation's most prevalent disorder, with 30.3 percent of the adult population reporting symptomatology that qualifies for an abuse or dependence diagnosis at some point in their lives (Hasin et al., 2007). Thus, the set of problems encompassed by this disorder is an extraordinarily large one.

A major point of this chapter is that the adult disorder does not emerge full blown in adulthood, but rather develops over time in a process for which childhood precursors are identifiable. To hone in on the early harbingers of this process, Figure 18.2 presents national data on past-month use, binge (≥5 drinks per occasion), and heavy use (≥5 drinks per occasion on ≥5 of the past 30 days) from the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2006). These data illustrate the sharp age-related increases in alcohol use and problem use as well as an estimate of the scope of early problem involvement. For example, among 15-year olds, 20% have engaged in recent alcohol use, 10% have engaged in a recent binge, and 2.5% are engaging in heavy drinking. To recast these figures, given that drinking for adolescents is heavily confined to weekends, this high-end group of 10% of 15-year-olds is reporting drinking at adult heavy drinking levels, and a fourth of that group is indicating that they are drinking at adult heavy drinking rates at most available opportunities. Using the new *DSM-5* criteria, and assuming any additional trouble related to the drinking (a not unreasonable assumption at this age), behavior sufficient to achieve a diagnosis of disorder has already been achieved by that group.

At the same time, it would be a mistake to presume that everyone with early signs of problem use will go on to develop adult disorder. The adolescent developmental literature has been clear that early alcohol use as well as alcohol problems need to be regarded as one component part of a deviance syndrome. The syndrome emerges in adolescence and is adolescent-specific in the sense that the majority of individuals with such problems do not go on to develop adult disorder, although some may reach diagnosable levels during their adolescent years (Blane, 1979; Donovan & Jessor, l985). Conversely, the problem prevalence figures, especially for those still in grade school, suggest that some etiologic factors have already been in place by the time middle school is started. Despite the ready availability of these incidence data, which drive the point home, this is not yet a widely known fact. Here and there one can find accounts in the clinical literature of the last generation, (e.g., Mitchell, Hong, & Corman, l979) which call attention to the occurrence of very early and severe child alcohol use. The effort to account for such beginnings

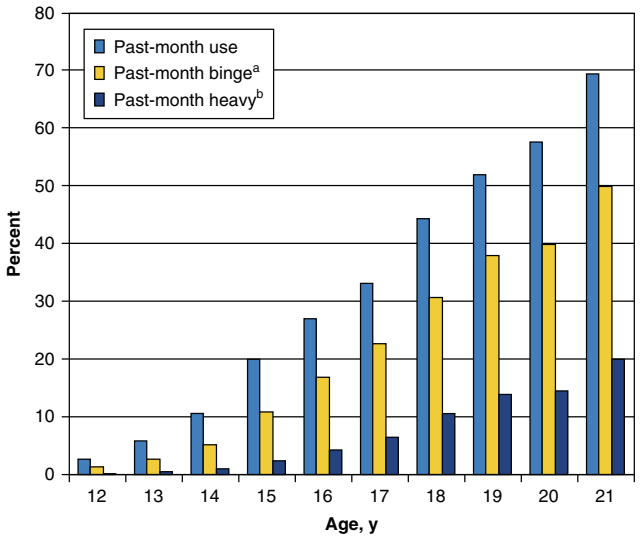


Figure 18.2 Past 30-day alcohol use (any, binge, or heavy) according to age. *Notes:* [a]Binge drinking was defined as ≥5 drinks per occasion; [b]heavy drinking was defined as ≥5 drinks per occasion on ≥5 days of the past 30 days. See footnote 1. Sources: Data from Substance Abuse and Mental Health Services Administration data from the 2005 National Survey on Drug Use and Health (SAMHSA, 2006). Figure reprinted from: A. S. Masten, V. B. Faden, R. A. Zucker, & L. P. Spear, Underage drinking: A developmental framework, *Pediatrics, 121,* S235–S251, 2008. doi: 10.1542/peds.2007–2243A PMID: 18381492

leads us to cast an etiologic net considerably earlier than adolescence. We do so later in the chapter, when dealing with the evidence about variations in risk and course of the disorder. However, this issue of differences in course, and a related set of questions about how many different variations there may be, what their determinants are, how best to describe and understand them, has become a major set of questions for the field because it encompasses issues of phenotypic heterogeneity as well as definitional issues about what the true nature of AUD might be. We also return to that set of questions later.

THE DEVELOPMENTAL PROGRESSION OF USE AND DISORDER: A MULTILEVEL MATRIX

Although it may seem a trivial point that one cannot have alcohol problems without the presence of alcohol, it is not trivial that such presence is regulated by societal norms about appropriate contexts of use, and the availability of the drug within society. At the same time, alcohol is not just a social object; it is also a drug, and understanding the pharmacodynamic and neurodynamic matrix of its action upon the human organism is also essential to understanding how the symptomatology of AUD comes to be. To chart the manner in which these causal structures interact requires model building that crosses multiple levels of analysis and multiple disciplines, operating over social, individual, and biological time (Cacioppo, Berntson, Sheridan, & McClintock, 2000). This perspective is inherent to a developmental psychopathological framework but it is not one regularly embraced by substance abuse researchers. To capture such a multilevel structure, a developmental systems framework (Cicchetti & Dawson, 2002) is essential as a means to organize these diverse levels.

The complexity of this multilevel network of systems makes it difficult to characterize as a unitary structure, but a few examples exist in the literature, including Sing and colleagues' elegant depiction of the developmental genetic architecture of complex diseases (e.g., Sing, Haviland, & Reilly, 1996) (see Figure 18.3) and at the opposite end of the biopsychosocial spectrum, Zucker's (2006) elaboration on Elder and Caspi's (1990) multigenerational linkage of individual, family, and historical events across three generations (see Figure 18.4). Although they are each incomplete, they convey a palpable sense of the multiple layers of system that operate a given point in time, that in turn change as time passes; they also convey how unspecified, and ultimately inaccurate, models are that purport to convey the mechanistic structure of addictive process but only operate within one or two of these systems (Cicchetti & Dawson, 2002). Perhaps the greatest challenge in these graphic representations is how to depict environment. The traditional view is that this is the simplest system of variation because its direction of influence is external to systems operating within the organism. It is often described only within the social domain, but it also encompasses the influences of social era and historical events (e.g., cataclysms, war) and to that extent surrounds all other mechanistic structures. Environment also operates internally, by way of variation in the neurohormonal, musculoskeletal, and organ systems, whose outputs are not all wired through brain (Maren, Phan, & Liberzon, 2013); to that extent, it is a system of influences that acts both externally upon the organism, and also internally, albeit in different ways.

Figures 18.5 and 18.6 provide a heuristic model of this multilayered system; it is laid out in this detail to allow specification both of targets of influence and also of timing of impact. As described here, it encompasses eight levels of analysis, involving genes, brain response/reactivity systems, the level of intermediate alcohol nonspecific phenotype (encompassing personality/temperament and behavior), environmental influences, depicted here as a unitary system, but capable of being disaggregated if the specificity of the variable network requires it (e.g., proximal social environment vs. interoceptive environment,

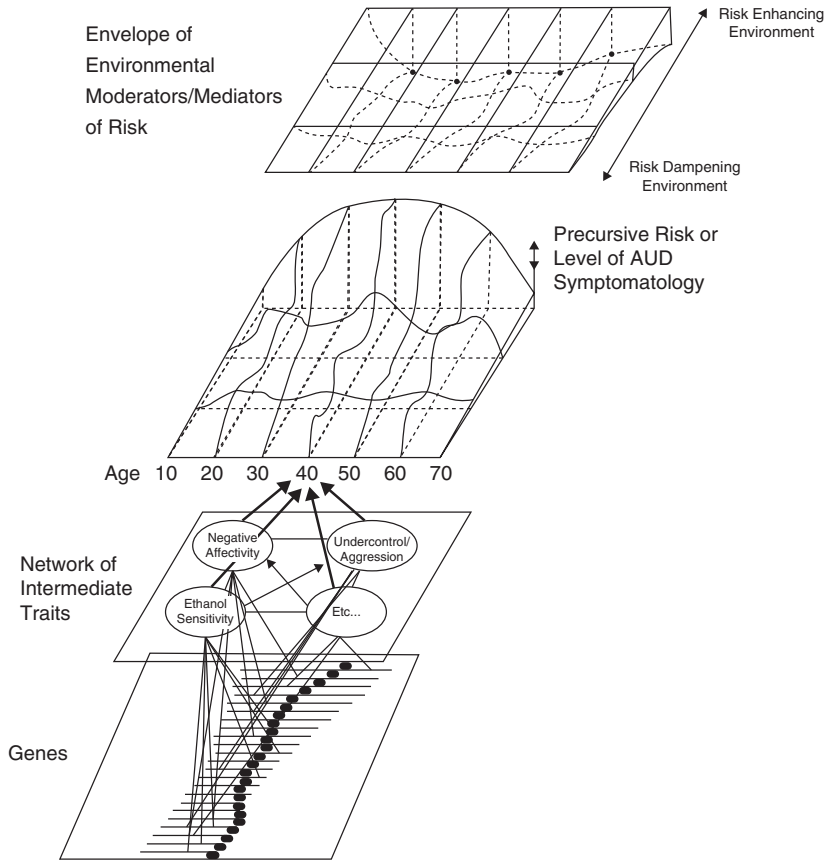


Figure 18.3 Probability of alcoholism (risk) over the life course: the envelope of risk expression as a function of genes, intermediate traits, environment, and life stage.

vs. distal (neighborhood, culture) environment, and time (both developmental and historical). Figure 18.5 diagrams the cross-sectional version of this multiply layered matrix, and Figure 18.6 is a crude depiction of the flow over time and across systems. The utility of this scheme is that it articulates the mechanistic scaffolding of a domain by charting the evidence for cross-level and cross-time connections, and it also identifies the connections that are currently unexamined. At the end of this chapter, we illustrate the utility of this matrix in characterizing multilevel gene–brain–behavior–environment relationships over the course of development.

VARIATIONS IN RISK AND COURSE OF DISORDER: ALCOHOL-NONSPECIFIC RISK, BEHAVIORAL DISINHIBITION, AND A HIERARCHICAL MODEL OF GENERAL AND SPECIFIC RISK FOR ALCOHOLISM

Not all of the casual structure for AUD is attributable to alcohol-specific processes. In fact, one of the historically most important findings of the past generation has been the repeated documentation of a link between an early and persistent pattern of antisocial behavior and earlier initiation of substance use and early onset substance use disorders (Donovan & Jessor, 1985). Earlier, we provided an overview of the work on problem behavior theory that emphasized the social psychological matrix for these differences. A parallel line of reasoning, driven strongly by a seminal paper by Tarter and colleagues (Tarter, Alterman, & Edwards, 1984), proposed that individual differences in temperament, ostensibly genetically mediated and relating to activity level, low attention span, and behavioral dysregulation are an essential early link in the chain of risk for alcohol use and problems in later childhood and adolescence. This temperamental substrate, coupled with an environmental structure that facilitates and even presses for the development of these initially neutral temperament attributes, is hypothesized to culminate in a behavioral adaption involving antisocial personality on the one hand, and a deviant peer network as a facilitating context on the other (Tarter et al., 1999; Zucker, Fitzgerald & Moses,

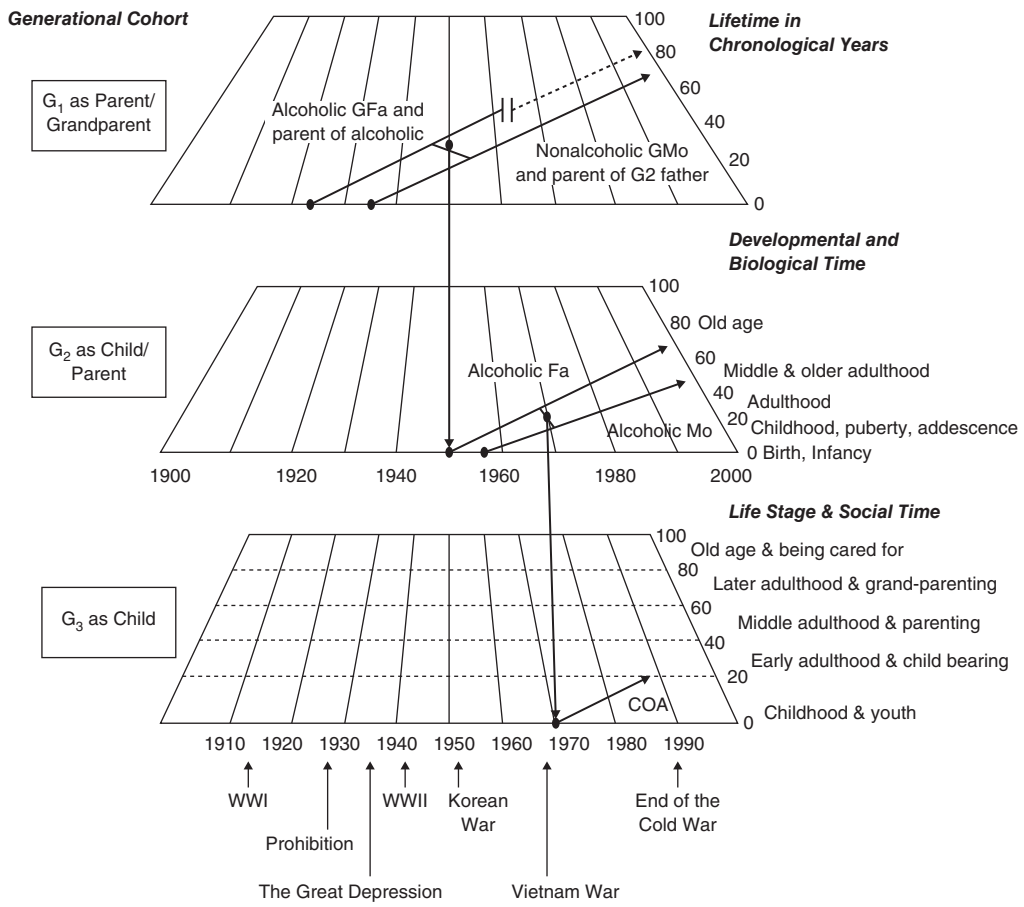


Figure 18.4 The multigenerational linkage of life-course trajectories in individual/developmental time, life-stage time, family time, and historical time: an example.

1995). These attributes are hypothesized to drive both initial alcohol use and the transition into early problem use.

Iacono, Malone, and McGue (2008) provided an updated summary of this line of research that conceptualized early onset substance use disorders as sharing common etiological influences with each other and other disorders, traits, behaviors, and neurological endophenotypes associated with behavioral disinhibition. Behavioral disinhibition was conceptualized as an inherited trait construct defined by an inability to inhibit socially undesirable or restricted actions. The phenotypic or observable manifestations of the behavioral disinhibition liability are typically referred to as externalizing behaviors, which include antisocial behavior, disinhibited personality traits, and substance use problems. The utility of the behavioral disinhibition model is that it helps to account for the high rates of co-occurrence among the various externalizing phenotypes. The model posits that a highly heritable behavioral disinhibition liability serves as a common diathesis, while environmental and disorder-specific influences (e.g., access to certain substances and not others, genetic sensitivity to certain addictive compounds) shape the final phenotypic expression of the general liability. This model then is ecumenical as it accounts for the high co-occurrence among externalizing phenotypes but also for why individuals develop some disorders and not others. Figure 18.7 depicts the Iacono et al. (2008) model of behavioral disinhibition and early-onset substance use disorders. The figure integrates the behavioral disinhibition liability, externalizing phenotypes, and environmental risk within a developmental context. A strength of the model is the hierarchical organization of general and specific risk factors, as well as its illustration of how the phenotypic expression of the behavioral disinhibition liability evolves over the course of development.

In childhood, behavioral disinhibition is evidenced by a collection of temperament traits—sometimes referred to as a difficult temperament (Tarter et al., 1985)—associated with undercontrolled behavior such as impulsivity, aggressiveness, hyperactivity, low frustration tolerance, lack of

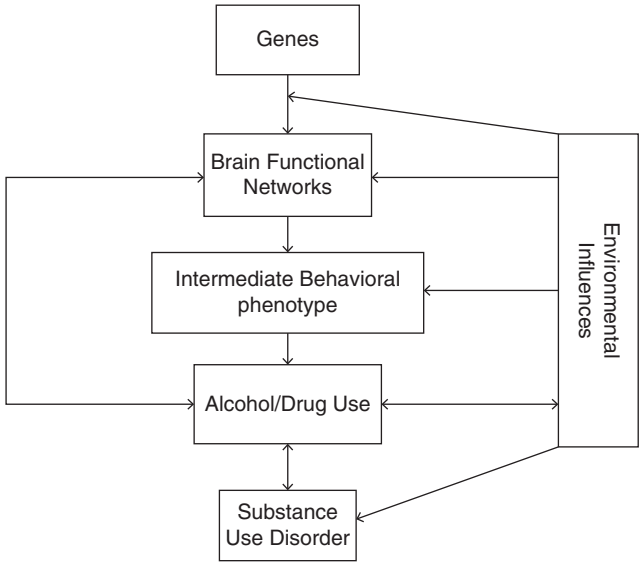


Figure 18.5 Cross-level/multidomain mechanistic structure of risk for alcohol use and AUD.

persistence, and inattention. Even in preschool aged children, these temperament traits have been associated with a greater familial loading for AUD, in particular, alcohol use problems of greater severity, duration, and comorbidity with antisocial behavior (Zucker, Ellis, Bingham, & Fitzgerald, 1996). Additionally, long-term prospective studies of both community and high-risk (e.g., children of alcoholics) samples have now verified that several of these trait markers of behavioral disinhibition that are present in preadolescence predict alcohol and other substance use problems in adolescence and young adulthood (Caspi et al., 1996; Cloninger et al., 1988; Dick et al., 2013; Hawkins et al., 1992; Hicks et al., 2014; Mayzer, Puttler, Wong, Fitzgerald & Zucker, 2002). The rate at which children mature and gain greater inhibitory control is also associated with risk for AUD, as those that are slower to do so are more likely to initiate alcohol and illicit drug use in adolescence (Wong et al., 2006). Further, as boys and girls transition into middle and later childhood, behavioral disinhibition takes the form of childhood disruptive behavior disorders including attention deficit hyperactivity disorder, conduct disorder, and oppositional defiant disorder. Consistent with the notion of a common liability, these disorders exhibit high rates of comorbidity, and are all associated with elevated risk for AUD and other substance use disorders in adolescence and adulthood (Iacono et al., 2008).

Continuing on the theme of nonspecific risk associated with behavioral disinhibition, the emergence of several problem behaviors in middle adolescence serves as an intermediate outcome linking externalizing behaviors in childhood to the eventual emergence of substance use disorders in adulthood (Jessor & Jessor, 1977). Such norm violating behaviors in adolescence include smoking, drinking alcoholic beverages, illicit drug use, delinquency, and precocious sexual behavior. Though the rate of these

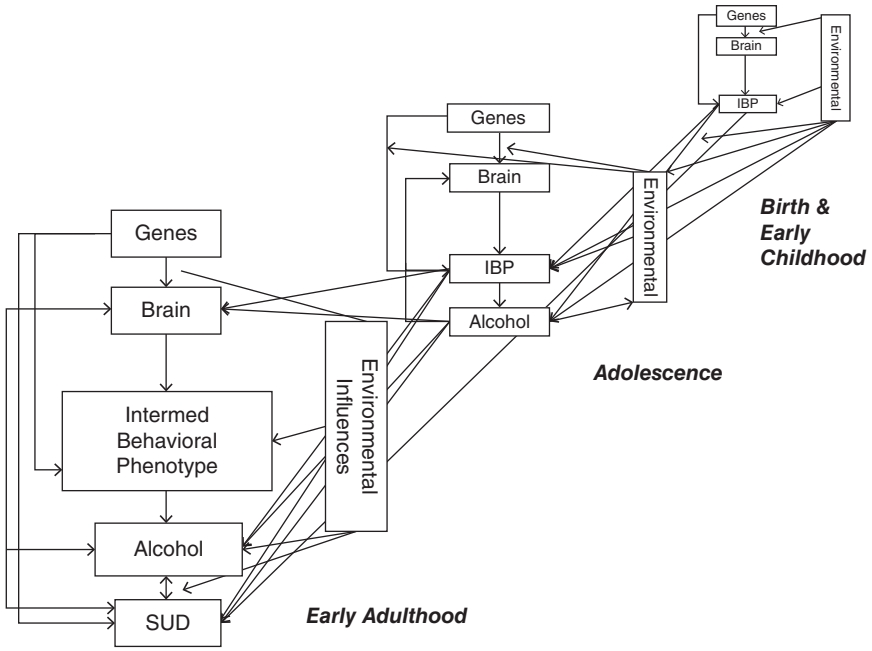


Figure 18.6 Multilevel mechanistic structure in developmental perspective.

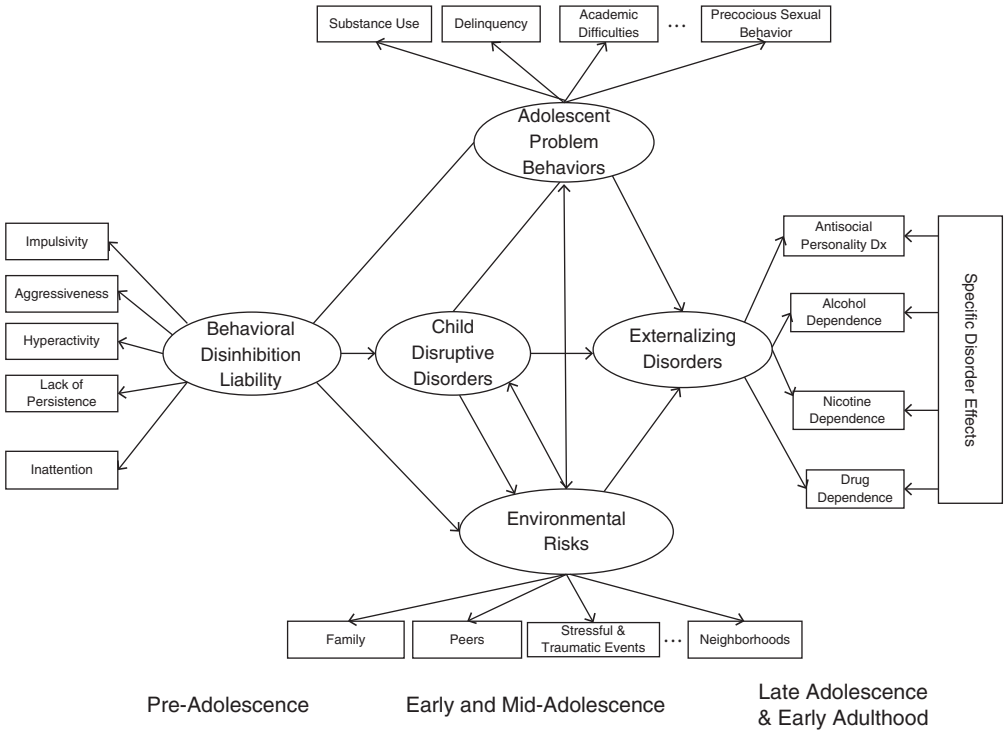


Figure 18.7 Model of behavioral disinhibition and early-onset substance use disorders. Note: the figure depicts the interplay among heritable individual differences characteristics and environmental influences on the development of three substance use disorders and antisocial personality disorder. Ellipses are latent variables that represent generalized risk factors. The variables in the boxes are conceptualized to represent specific and observable manifestations of these generalized risk factors. Specific genetic and environmental effects represented by the box at the far right work to differentiate the adult disorder from one another. Dots between the boxes are meant to indicate that other risk factors in addition to those depicted in the figure contribute to the development of substance use disorders. *Source:* Figure adapted from W. G. Iacono, S. M. Malone, & M. McGue, Behavioral disinhibition and the development of early-onset addiction: Common and specific influences, *Annual Review of Clinical Psychology, 4*, 12.1–12.24, 2008.

behaviors increases dramatically over the course of the teenage years, their early emergence—typically defined as prior to age 15—is associated with a substantial increase in the rate of AUD in adulthood. For example, Grant and Dawson (1997) found that initiation of alcohol use prior to age 15 was associated with a four-fold increase in risk for a lifetime AUD relative to persons who initiated alcohol use at age 20 or later. Rather than a causal factor per se, however, the evidence seems to favor a nonspecific mechanism of risk, with these problem behaviors being age appropriate markers of disinhibition. Focusing on an early initiation of alcohol use, McGue, Iacona, Legrand, Malone, and Elkins (2001) found that age of first drink predicted not only AUD but also nicotine dependence, illicit drug dependence, and antisocial personality disorder in adulthood, and was associated with an undercontrolled temperament, disruptive behavior disorders, and academic difficulties in preadolescence. McGue and Iacono (2005) went on to demonstrate that delinquency and initiation of alcohol, nicotine, illicit drug use, and sexual intercourse prior to age 15 all predicted not only AUD but also nicotine dependence, illicit drug dependence, and antisocial personality disorder at age 20. These findings were again consistent with the notion that adolescent problem behaviors represent an intermediate outcome along the behavioral disinhibition pathway to adult externalizing disorders.

The culmination of the behavioral disinhibition pathway is the emergence of full-blown substance use disorders and antisocial personality disorder in late adolescence and young adulthood. Consistent with the high co-occurrence among the different externalizing phenotypes present at earlier developmental stages, these disorders also exhibit high rates of comorbidity. Similar to models of childhood psychopathology (Achenbach, 1991), this externalizing factor is typically juxtaposed to a latent internalizing factor that accounts for the comorbidity among unipolar mood and anxiety disorders (Krueger & Markon, 2006). The behavioral disinhibition liability is often conceptualized as being a primary contributor to the comorbidity among the adult externalizing disorders. Interestingly, however,

the importance of this general liability in accounting for risk in the individual disorders seems to peak in late adolescence and then decline throughout adolescence (Vrieze, Hicks, Iacono, & McGue, 2012). People tend to be nonspecific in their substance use and abuse in adolescence, but tend to become more specialized in their drug use as they transition from young to middle adulthood. As such, disorder-specific factors become more important in the maintenance of addictions over time. These findings emphasize the hierarchical and ecumenical nature of the model. That is, behavioral disinhibition is not meant to account for every case of AUD; rather, the common disinhibition liability provides an organizing framework that incorporates both nonspecific risk that contributes to several correlated outcomes, that along with disorder-specific risk factors shapes the final phenotypic expression of substance use problems.

Environmental Risk: General and Specific

Environmental influences are also a key part of the behavioral disinhibition model and play a crucial role in development of AUD and other externalizing disorders (Hawkins et al., 1992). Similar to the hierarchical structure of externalizing symptoms, environmental risk can also be organized into influences associated with externalizing disorders in general, and environmental influences that have more specific effects for a given disorder (Bailey, Hill, Meacham, Young, & Hawkins, 2011). In fact, most of the environmental risk factors associated with AUD are associated with risk for externalizing disorders in general. For example, prenatal exposure to alcohol and drugs is associated with increased rates of conduct problems and alcohol and illicit drug use problems in adolescence (Baer et al., 2003). Childhood physical and sexual abuse is also associated with increased psychopathology in general including substance use disorders (Kendler et al., 2000). Several aspects of the family environment are also risk factors for conduct problems, antisocial behavior, and substance use problems including poor parent–child relationship quality, harsh and inconsistent discipline, and lack of parental monitoring (Granic & Patterson, 2006; Masten et al., 2008). Disinhibited children often experience difficulties in academic contexts related to both achievement and discipline, problems that tend to emerge early and persist through adolescence (Hawkins et al., 1992). Characteristics of a child's peer group are also strongly associated with antisocial behavior and substance use problems. Disinhibited children are often rejected by prosocial peers, and so tend to become isolated and depressed. As a consequence, disinhibited children tend to associate with each other, forming deviant peers groups that reinforce a culture of norm violation, potentiating individual risk factors (Dishion & Owen, 2002). A child's broader ecology such as aspects of their neighborhoods like poverty, residential instability, and crime rates are also nonspecific risk factors for antisocial behavior and substance use problems (Buu et al., 2009).

It is important to note that exposure to these different risk factors is not independent, that is, exposure to one risk factor increases the likelihood of exposure to another (Appleyard et al., 2005; Hicks et al., 2009). Further, exposure is disproportionately spread across the population such that a small number of people experience an especially high density of risk exposures. Additionally, the mechanism by which environmental variables increase risk for AUD and other externalizing disorders appears to be cumulative. That is, multiple rather than single exposures over time tend to be the norm, with the number of risk factors rather than the specific form of risk being the most important factor in the development of antisocial behavior and later substance use problems.

These contextual influences tend to carry over into adulthood. That is, as adults, formally disinhibited children tend to select into environments that help to maintain a pattern of maladaptive alcohol use (Masten et al., 2008). For example, persons whose AUD persists past young adulthood tend to maintain peer groups with norms for both frequent drinking and heavy drinking. Also, relative to the intimate partners of people whose AUD symptoms desist and drinking habits normalize by young adulthood (age 30), the intimidate partners of people who exhibit chronic alcohol use problems typically drink larger quantities and have more tolerate attitudes toward substance use (Hicks, Iacono, & McGue, 2010). Also, people with persistent AUD tend to remain in or migrate into disadvantaged neighborhoods as defined by high rates of crime, poverty, and residential instability (Buu et al., 2007). Transactional processes then between persons and situations contribute to the stability of the broader risk structure that helps to maintain AUD over the long term.

In addition to the nonspecific effects of many environmental variables, there are also a number of risk factors that are specific to AUD and other substance use disorders. The drinking patterns of parents and older siblings provide both norms regarding appropriateness of drinking as well as potential points of access, especially for underaged children. Bailey et al. (2011) found that the family drinking environment predicted AUD specific variance (i.e., independent of externalizing) after accounting for measures of

the general family environment. More generally, the social environment (context) plays a role in cueing (triggering craving), and in providing greater or lesser availability of the drug. Alcohol involvement within a heavy using social context is a significant element precursive to establishment of disrupted reward process, as well as influencing the probability that remission will or will not take place among recovering individuals. The epidemiologic literature provides some well-known examples of these effects. For one, the wetness or dryness of the society (Skog, l985) changes the threshold within which alcoholism will appear (Reich, Cloninger, Van Eeerdewegh, Rice & Mullaney, l988); a wetter society increases the rate of AUD in its population, and a drier one decreases it. Another longer term effect is that a lower level of genetic susceptibility is more likely to be expressed in higher as compared to lower consumption societies since drinking rates will be higher in the higher consumption environment. Under those circumstances, even persons with the lower susceptibility will be more likely to move into diagnosis because they are more likely to drink heavily due to greater environmental cueing (also see Rose, Kaprio, Winter, Koskenvuo, & Viken, 1999 for another example of such interactions).

Change in rates of heavy use as a function of change in legal age of access to alcohol is still another such example. Thus, drinking and driving accidents and loss of life during the 18 to 20 period noticeably decreased as a result of legislation moving the legal age to 21 (Wagenaar & Toomey 2002). The spread of effect beyond age 21 gives some sense of the long lasting impact of the change. Lower drinking rates were also found in the subsequent 21–25-year-old age period (O'Malley & Wagenaar, l991). More recent work has also shown lasting differences in drinking outcomes for those living in the era before the age 21 limit was in effect as compared to those living in the years thereafter, who were exposed to the legislation. Even when in their 40s and 50s, the nonexposed group had higher rates of both alcohol use disorder and other substance use disorder (Norberg, Bierut, & Grucza, 2009). Ultimately our models of process need to incorporate these cohort exposure variations as well.

Is There an Internalizing Pathway to AUD?

In addition to behavioral disinhibition, internalizing distress is hypothesized to be another precursor to AUD (Hussong et al., 2011). In the adult literature, internalizing typically refers to diagnostic symptoms of unipolar depression and anxiety disorders along with personality traits such as neuroticism and negative emotionality. In early childhood, this liability is expressed as a cluster of traits that includes lack of approach and exploratory behavior, passivity, flat affect, discomfort with novelty, shyness/social fearfulness, and anxiety when separated from caregivers (Capsi et al., 1996; Fox et al., 2005). This inhibited temperament predicts depression, anxiety disorders, and negative emotionality in childhood and adolescence (Capsi et al., 1995, 1996), which are correlates of substance abuse as well as predictors. The prospective associations between inhibition and substance abuse/AUD in adolescence and adulthood have been found in a number of prospective studies in addition to that of Caspi et al. (1996) (compare to Cloninger et al., 1988; Hawkins et al., 1992; Mayzer et al., 2002). The relationships are modest, however, especially after accounting for externalizing, and seem stronger for depressive and social inhibition indicators than for anxiety symptoms (Chassin et al., 1999; Kaplow et al., 2001; King et al., 2004). Interestingly, some investigators have found that inhibition/internalizing in childhood predicts abstaining from substance use in adolescence (Shedler & Block, 1990), while others have found a negative association with substance use/abuse in adolescence and adulthood (Cloninger et al., 1988; Kaplow et al., 2001). This suggests that different aspects of inhibition/internalizing have differential associations with substance use and abuse (e.g., lower risk for social fearfulness and discomfort with novelty, higher risk for depression and stress reactivity; Kaplow et al., 2001).

Recently, two research teams working independently reported similar findings that childhood temperament/personality traits associated with *low* internalizing predicted substance use and abuse in adolescence. Dick et al. (2013) factor analyzed temperament ratings of over 12,000 children in the UK that were assessed on multiple occasions from 6 months to 5 years old and identified two largely uncorrelated temperament dimensions. One was called *emotional and conduct difficulties* and seemed to tap externalizing. In contrast, the other trait called *sociability* was characterized by lack of shyness and high social engagement and activity. Sociability predicted both alcohol use and alcohol problems at age 15.5 over and above emotional and conduct difficulties, with the effects of sociability partially mediated by the later emerging personality traits of extraversion and sensation seeking and selection into antisocial peer groups in emerging adolescence (ages 10.5–13).

Using a very different approach, Hicks et al. (2014) reported similar findings in a large sample of twins born in Minnesota that were first assessed at age 11. Specifically, they used an empirical approach to identify the traits and

behaviors present prior to initiation of substance use that best predicted substance use problems at age 17. The first trait was called *socialization* and was characterized by a propensity to conform to rules, endorse conventional values, and accept adult supervision. Low socialization had strong associations with childhood disruptive behavior disorders, parental externalizing disorders, and a composite of environmental risk. Hicks et al. then found that a trait called *boldness*—characterized by social dominance and social engagement, stress resilience, and thrill seeking—best-predicted substance use problems after accounting for socialization. Boldness was uncorrelated with socialization, childhood disruptive behavior disorders, and parental externalizing disorders and had negative associations with internalizing and a composite of environmental risk. Also, boldness was highly heritable (.71), while socialization exhibited both moderate heritable (.45) and shared environmental (.30) influences (i.e., environmental influences that contribute to similarity among relatives). Though socialization had a larger effect ($r = -.44$), boldness exhibited a small but robust ($r = .22$) incremental effect in predicting a composite of substance abuse in adolescence and young adulthood in both the development sample and a replication sample. Follow-up analyses showed that much of the effect of childhood socialization on substance use problems in late adolescence was mediated by selection into high-risk environments in middle adolescence (Hicks et al., 2013, 2014). In contrast, boldness had a direct, genetically mediated effect on substance abuse that was largely independent of the environmental context in childhood and middle adolescence.

The consistency of the results reported by Dick et al. (2013) and Hicks et al. (2014) are striking given the different approaches to identify personality traits, the different ages and nationalities of the samples, and the large sample size and sophisticated measurement and follow-up assessments of each study. Clearly, in terms of childhood characteristics that increase risk for alcohol and other drug use and abuse, there is something beyond externalizing, but it does not appear to be internalizing per se. Rather, the convergence of sociability, social dominance, stress immunity, and thrill seeking seems to increase risk for substance abuse while also decreasing internalizing. Conceptually, the sociability and boldness constructs identified in these reports are similar to low behavioral inhibition, a trait defined in young children by low social and object fear and ease in novel, uncertain, and potentially frightening situations (Fox et al., 2005). Also, Patrick, Fowles, and Krueger (2009) posited that a boldness trait characterized by high self-assurance and social efficacy, resilience to stress and coolness under pressure, and tolerance for unfamiliarity and danger underlies the interpersonal facets of psychopathy that have been associated with reduced fear-potentiated startle. Low fear-proneness is hypothesized to be the genotypic disposition underlying both low behavioral inhibition and psychopathic boldness, which are potential phenotypic expressions of constitutional fearlessness. Low temperamental fear as expressed in interpersonal contexts and a proclivity for venturesomeness then may be a temperamental risk factor for substance use problems that is relatively independent of the behavioral disinhibition liability, although it is the obverse of social inhibition.

While the findings for boldness offer an interesting new direction, the link between internalizing and alcohol use problems remains unclear. Though childhood internalizing may not increase risk for substance use problems, internalizing may moderate (i.e., magnify) the influence of externalizing traits. Alternatively, the link between internalizing and alcohol use problems may primarily be present as a function of adult psychopathology. For example, heavy alcohol use may be used to reduce the feelings of negative affect associated with social anxiety or trauma-related symptoms of posttraumatic stress disorder. This is more likely to take place in adulthood, when the social inhibition and reticence associated with high anxiety may not be sufficient to curb the need to find relief. At that point, heavy alcohol use may come into play. (See Section 5 discussion of negative affect alcoholism.) Also, internalizing may play a stronger role in the onset and maintenance of alcohol use problems for women relative to men. Whatever the case, the link between internalizing and alcohol use problems in adolescence and young adulthood is complex, such that longitudinal analyses that can clearly track their co-development are necessary to better understand the nature of their relationship. In addition to the broad internalizing and externalizing dimensions, there is some evidence that childhood sleep problems are also associated with later substance use and abuse. Wong et al. (Wong, Brower, & Zucker, 2009) observed a relationship between ratings of sleep problems at age 3 to 5 and early onset of drug use (alcohol, cigarettes, marijuana, other hard drugs). The relationship remained even when a number of other plausible mediators, including family history of alcoholism and externalizing problems (specifically, attention problems and aggression) were added into the predictive model. In other words, sleep difficulties very early in life appear to be a marker of an independent contributor to early substance involvement. Given that early alcohol use has repeatedly been identified as a proxy for elevated later risk of alcohol dependence, as well as a host

of adolescent problems including injuries, violence, and drunk driving (Gruber, DiClemente, Anderson, & Lodico, 1996), these data support a third risk pathway. Although a self-medication hypothesis, a negative emotionality hypothesis, or a central dysregulatory deficit hypothesis are all plausible mechanistic explanations for the internalizing effect, the mechanisms undergirding that relationship remain to be disaggregated.

Heterogeneity in the Course of Risk: Heterogeneity of Nonspecific Risk

As just discussed, although behavioral disinhibition expressed as early and persistent antisocial behavior is the most robust and reliable predictor of substance use problems, it remains only one of a number of risk factors that contribute to AUD. In fact, the majority of people with AUD do not exhibit a persistent pattern of antisocial behavior, indicating that there are multiple pathways that lead to AUD and that the category likely includes several subtypes based on differing etiological factors. Equifinality is a well-known systems theory concept wherein multiple, sometimes linked and sometimes disparate processes engage in a way that produces a common phenotypic endpoint. The core etiologic question then is how do people with distinct risk profiles reach this common outcome, and to what degree will their longer-term developmental trajectories converge or diverge over time?

We illustrate the interplay among key risk factors of externalizing, internalizing, and family adversity over the course of developmental by summarizing work from the Michigan Longitudinal Study (MLS; Zucker et al., 2000, Zucker, 2014). This longitudinal, high-risk for substance abuse family study has followed alcoholic men, their spouse and children, and a suitably matched but nonalcoholic set of contrast families drawn from the same high risk neighborhoods where the alcoholic families lived. All family members were assessed at 3 year intervals beginning when the target boy was 3–5 years old. A person-centered approach was used to examine the joint effects of family adversity and child risk vulnerability from ages 3 to 14 years. The adversity index assessed level of family pathology and included the severity of AUD and the presence or absence of antisocial behavior in each parent (cf. Wong, Zucker, Fitzgerald, & Puttler, 1999; Zucker et al., 2003). Although based on parental psychopathology, this index is an effective proxy for a number of other pertinent indicators of family adversity, including greater conflict, violence, economic difficulty, family crises, other psychiatric comorbidity, and trouble with the law (Zucker et al., 1996b).

The child's initial risk status at ages 3–5 was assessed with the Total Behavior Problems scale of Achenbach's Child Behavior Checklist, a global psychopathology measure that is nationally normed. Low risk was defined as being within normal limits on this index, high risk was defined as being at the 80th percentile or higher on the measure. A 2 x 2 grid was created by crossing family adversity and child behavior problems. *Resilient children* were defined by having normal to high adaptation (i.e., low risk scores) even though they were living in high adversity families. The normal risk under conditions of low family adversity group was labeled *nonchallenged* to emphasize that their behavior was unremarkable within families of low adversity that were more likely to be nurturant and encouraging. Children with high problem behaviors under conditions of high family adversity were labeled *vulnerable*, to emphasize both the continuing exposure to family difficulty and the likely high genetic load for substance use disorder. Lastly, children with high behavior problems under conditions of low family adversity were characterized as *troubled* to emphasize poor behavioral adaptation, even without the pressures of family adversity.

Figure 18.8 shows the trajectory of externalizing problems for each of the groups, and Figure 18.9 shows the trajectory of internalizing problems from preschool to early adolescence. Overall across-age group differences were significant for both externalizing and internalizing problem trajectories. The nonchallenged group sustained the lowest level of externalizing problems over the course of childhood and early adolescence, followed by the resilient

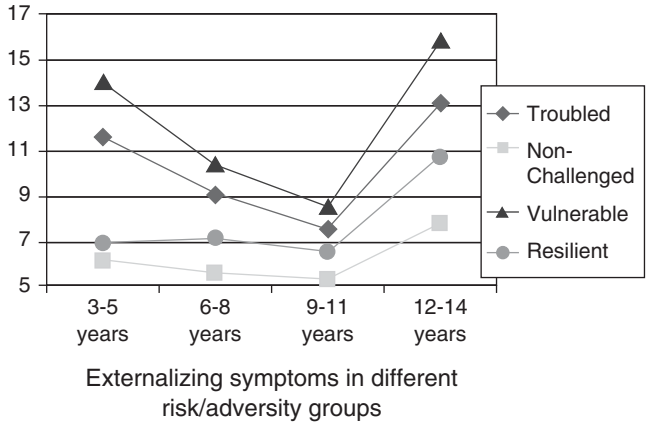


Figure 18.8 Externalizing symptoms in different risk/adversity groups. *Source:* R. A. Zucker, M. M. Wong, L. I. Puttler, & H. E. Fitzgerald, Resilience and vulnerability among sons of alcoholics: Relationship to developmental outcomes between early childhood and adolescence, in S. Luthar (Ed.), *Resilience and vulnerability: Adaptation in the context of childhood adversities* (p. 88), New York: Cambridge University Press, 2003. Reprinted with permission.

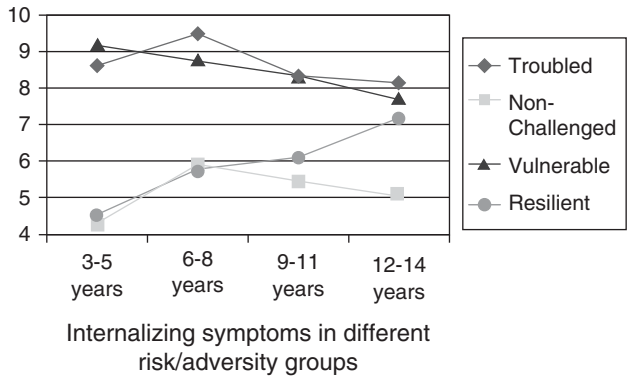


Figure 18.9 Internalizing symptoms in different risk/adversity groups. *Source:* R. A. Zucker, M. M. Wong, L. I. Puttler, & H. E. Fitzgerald, Resilience and vulnerability among sons of alcoholics: Relationship to developmental outcomes between early childhood and adolescence, in S. Luthar (Ed.), *Resilience and vulnerability: Adaptation in the context of childhood adversities* (p. 88), New York: Cambridge University Press, 2003. Reprinted with permission.

group, the troubled group, and the vulnerable group. Externalizing scores tended to decline over childhood (normative for this age range; Loeber, 1982), and there was increasing convergence in externalizing scores across the groups through middle childhood. At the transition to adolescence, the normative pattern of a developmental shift involving increased externalizing behavior was present (cf. Jessor & Jessor, 1977). Though the resilient children were not different from their nonchallenged peers as preschoolers, they showed more externalizing problems as they grew older. That is, a small but detectable convergence with the other initially more externalizing two groups starts to become manifest. At the same time, they still occupied an intermediate place, having a lower level of these behaviors than did their vulnerable peers. Additionally, the divergence of slopes between ages 9 to 11 and 12 to 14 involved a significant interaction between children's initial risk and level of family adversity. That is, externalizing problems increased more for children with the greatest initial risk status and family adversity during a period of life when the overall norm is for increasing deviant and impulsive activity.

Figure 18.9 shows the trajectories for internalizing problems; here also the nonchallenged group had the lowest scores, followed by the resilient group. Scores for the troubled and vulnerable groups were similar to each other. The figure also shows important pattern variations. During preschool and up through the early school years, nonchallenged and resilient children were significantly lower in internalizing symptoms than both the vulnerable and troubled groups, and there were no differences between the resilient and the nonchallenged children. The pattern begins to diverge following second to third grade, and by early adolescence the nonchallenged group is significantly lower than all others, and no differences exist between any of the other three groups. In other words, at this juncture the resilient children had developed a level of internalizing symptoms that was similar to both the vulnerable and the troubled children. A significant interaction effect of time and adaptation group indicated that the developmental trajectories of internalizing problems varied differently among the adaptation groups, with three of the four showing a continuity pattern, and one a discontinuity pattern.

At a more phenomenological level, the internalizing trajectory pattern of the resilient group implies that a weathering process had been taking place, wherein an initially happier adaptation gives way to the sustained exposure to an adverse, more conflictual environment involving more family stress and disruption. The result, by early adolescence, is that the level of internalizing behavior for this group was indistinguishable from the initially more troubled and vulnerable children. These data provide a poignant illustration of how the shift from normal to pathological adaptation may take place under circumstances of sustained adversity. Recall, however, that this shift only occurs in the more covert, internalizing behavior domain; the more obvious externalizing behavior differences remain, with the resilient children sustaining a pattern that differentiates them from their vulnerable and troubled peers.

The trajectory variations reflect more than just differences in nonspecific risk over time. They also are proxies for differences in probability of eventual problem drinking, other problem behavior, and alcohol dependence (Ellickson et al., 2003; Grant & Dawson, 1997). In the Michigan study, Mayzer and colleagues (2009) confirmed the first step in this chain of effect by showing that higher levels of early externalizing and internalizing behavior were predictive of both early onset of drinking, as well as higher levels of externalizing and internalizing behavior and delinquent activity in adolescence. But several steps in the causal structure are still not well enough understood. We have already discussed this caveat vis-à-vis the internalizing pathway in the section just preceding. However, a qualifier also exists for the predictive power of the externalizing pathway. Other analyses have shown that the level and rate of change of externalizing problems are partially attributable to an active environment including parental conflict and harsh and inconsistent discipline (Fuller et al., 2003; Loukas, Zucker, Fitzgerald & Krull, 2003). However, these studies cannot disentangle the nesting of high child risk in high biological risk families. It is possible that the

higher levels and persistence of problem behaviors that appears to be a socialization effect is actually the result of indirect genetic effects?

Recently, Trucco and colleagues (2015) extended these findings in two ways: by (1) using an empirical approach to parse the heterogeneity of nonspecific risk in adolescence in the MLS; and (2) by examining the interplay between genetic, personality, and environmental risk factors). Growth mixture modeling was used to evaluate whether there were distinguishable trajectory classes of externalizing problems over the course of adolescence (12–17). Additionally, the work examined the impact of parental monitoring and variants of the GABRA2 gene, a gene located on chromosome 4 that codes for the alpha-2 sub-unit of the receptor of the neurotransmitter GABA-A. Variants of GABRA2 have been associated with both AUD and externalizing behavior, and the interaction between parental monitoring and GABRA2 variants predicts trajectory classes of externalizing problems in childhood and adolescence (See also Dick et al., 2009).

In the Trucco study, three trajectory classes provided the best fit to the data. The majority of adolescents (77%) exhibited consistently low levels of externalizing. A small subset (10%) had higher initial levels of externalizing that decreased across adolescence. The last group (13%) had moderate initial levels of externalizing that increased at a nonlinear rate throughout adolescence. Both parental monitoring and parental AUD increased the odds of being in the decreasing or increasing externalizing groups relative to the low externalizing group. Further, there was an interaction between parental monitoring and *GABRA2* genotype such that carriers of the minor allele were more likely to be in the increasing externalizing trajectory in the context of low parental monitoring relative to the decreasing and consistently low trajectory groups. These results provide an excellent illustration of the interplay among genetic, environmental, and developmental influences on precursive risk for alcohol use problems that ultimately contributes to the relatively distal outcome of AUD.

VARIATIONS IN RISK AND COURSE OF THE DISORDER: EMERGENCE AND COURSE OF ALCOHOL-SPECIFIC RISK

When Does Risk for Alcohol Involvement Begin?

It is extremely rare to see a 5-year-old consuming alcoholic beverages, given that the normative expectation among youth, as well as the modal behavior in American society, is for self-initiated drinking of alcoholic beverages to commence around age 14. The problem use figure also slowly moves upward with age, with 16% of tenth graders, 25% of twelfth graders, and 40% of college students reporting binge use in the prior 2-week period. (Johnston, O'Malley, Bachman, & Schulenberg, 2009). At the same time, age progression is, of itself, not an explanation of process but rather a chronological marker of other events that lead to onset or problem use. Individual differences in age of onset are attributable to differences in the rapidity of emergence of the underlying causal event structure. The developmental question is one of specifying the events and circumstances under which they show up.

From this perspective, neither first drinking experience nor first bingeing experience are the beginnings of the process of alcohol involvement, or of the emergence of alcohol problems, abuse, and dependence. Alcohol has a place in the ritual practices of many religions, and thus allows children to have minor consumption experience well before they have made any conscious decision to drink (Hanson, 2013). Even more so, media exposure assures that some knowledge of alcoholic beverages is present well before peers offer the opportunity for drinking to take place (Smith & Foxcroft, 2009). More generally, for regular (volitional) drinking to take place, the child implicitly needs to be aware that there is a class of substances, collectively known as alcoholic beverages, and that these substances have certain properties (effects) connected to their ingestion. This involves the development of an alcohol schema; i.e., a concept containing knowledge of the features or attributes of the object and the situations in which it comes into play (Baldwin, 1992). It also involves the development of a set of cognitions—expectancies—about the situations and manner of use. These expectancies need not all be explicit; some are not verbalizable, but they play independent roles in guiding/directing the behavior (Reich, Below & Goldman, 2010). They need to be sufficiently favorable/positive to motivate the individual to engage in alcohol seeking (or at least alcohol accepting). These properties, collectively known as implicit cognitions (Weirs & Stacy, 2006) and outcome expectancies (Goldman, Reich, & Darkes, 2006), have been shown to be direct effect predictors of both alcohol and other drug use (Andrews, Tildesley, Hops, Duncan, & Severson, 2003; Stacy & Weirs, 2010).

The theoretical base for this work has been the social cognition and memory process literatures (e.g., Tiffany, l990) which has emphasized not only the representational but also the motivational attributes of internally constructed cognitive models (schemas) (Ajzen, 1991). From

the perspective of the observer, the actual decision-making may appear too rapid for this to occur. But a now voluminous literature involving carefully controlled laboratory studies has shown how the underlying details which shape the decision making can be identified. A complex interplay of affective as well as rational elements is factored into the subjective equations that underlie ongoing drinking behavior, as well as the decision-making about whether one should initiate drinking in specific situations, or refrain (Stacy & Weirs, 2010). The developmental question is, how and under what conditions are these elements learned?

Within this conceptual tradition, and using methods that allow young children to tell the experimenter about their knowledge of the rules that govern alcohol use, a number of developmentally early focused studies have shown that preschoolers in the general population already know two of the core alcohol use schemas of the larger culture: the children, even at age 3 to 5, already attribute alcoholic beverage consumption more to adults than children, and more to adult males than adult females (Noll, Zucker, & Greenberg, 1990). In addition, the ability to identify alcoholic beverages by smell (an indicator of personal exposure rather than simply media exposure) was both age graded and also based on experiences going on in the home. Older children were better at identifying these beverages than younger ones, and the ability to recognize alcoholic beverages was directly related to the amount of alcohol the parents consumed, as well as the degree to which their parents' reported use of alcohol for escape reasons (Mennella & Foresell, 2008; Noll et al.,1990).

A logical extension of this work is the examination of possible differences in schema structure in high risk populations such as children of alcoholics (COAs), for it is here that exposure differences would be most likely expected, and also where the early identification of risky cognitions would be anticipated to be of greatest long term significance. Zucker, Kincaid, Fitzgerald and Bingham (1995b) explored this possibility by examining differences in alcohol use schemas in preschooler COAs and suitably age matched children from nonalcoholic homes. They asked children to identify photographs of alcoholic beverages, and also examined the degree to which alcoholic beverage use was attributed to people depicted in common situations where beverages are consumed (e.g., at a meal, on a picnic, at an adult party). COAs were more likely to identify at least one alcoholic beverage, and were better able to correctly identify specific alcoholic beverages. Differences in the children's attributions of alcoholic beverage use to adults were again predicted by their parents' reported level of alcohol consumption. In short, alcohol schemas relating to both knowledge and use were more common in the alcoholic families.

Mennella and colleagues (1998, 2008), in a series of interesting studies, have also shown that children's exposure to alcohol in the home has significant effects on their response patterns and opinions. Mennella and Beauchamp (1998) found that children's opinions about alcohol (mouthing or not mouthing a toy among infants; liking or not liking the smell of alcohol in primary graders, is related both to level of consumption by the mother, and age of the child. Young children with escape drinking mothers were more likely to mouth a toy that was alcohol scented than those whose mothers were nonescape drinkers. In another study in the series, among early school graders, although children from both types of drinking homes identified the beer smell equally well, children of escape drinkers were more likely to dislike the smell (Mennella & Garcia, 2000). Further, children of escape drinkers took longer to decide whether they liked the odors than children of nonescape drinkers.

In a mechanistic sense, the relationships of olfactory stimuli to neural circuitry are of considerable importance. As noted by Menella and Forestell (2008):

> Unlike other sensory systems, the first cortical relay is not the thalamus but rather the primary olfactory cortex which then links with the amygdala-hippocampus complex of the limbic system. The unique processing of olfactory information and the olfactory system's immediate access to these neurological substrates underlying non-verbal aspects of emotion and memory explains why verbally identifying an odor [is] a more difficult task for children than deciding whether they like the odor. (P. 252)

It also provides another reason that early learning about alcohol is so closely tied to the child's later behavioral experience. Given the importance of this circuitry in later childhood and adolescence in determining reward responsivity and affective response, it also raises the interesting question of whether there might be some interactive relationship between such early exposure and later risk responsivity. This issue has not been examined.

Taken together, these studies indicate that there is a steady path from the very earliest learning about alcohol to the emergence of rudimentary schemas, initially one characterized by the ability to recognize the object, moving on into the development of a set of cognitive schemas about how the object/substance is used by others, and developing thereafter into an implicit and explicit expectancy structure about use. The social environment plays a major role in this process insofar as the presence of drinkers/heavy drinkers stimulates earlier movement

through this sequence. The experience of frequent exposure and easy availability set the stage for an expectancy structure that is positive, and this in turn is an important feature that primes the individual to be open to use, and possibly also to seek out use, when the opportunity presents itself. Conversely, involvement in a social environment where youth drink moderately or not at all, makes the nondrinker much less likely to begin, and if experimenting, much less likely to move into more regular use. At the same time, as described previously, individual differences in nonspecific risk are also priming the individual to engage in (or refrain from) drinking. These personality/temperament differences shape the choice of peers, which will both make the social environment a heavier (or lighter) using one, and also make access to alcohol (and other drugs) more or less available. In addition, individual differences in sensitivity of response to the drug's intoxicating effects also play a role in dampening or enhancing the movement into a heavier drinking career (Schuckit et al., 2001). Low sensitivity of response allows the individual to drink more without noticeable effect. Moreover, some individuals are energized by consumption, others find it soporific, and still others find the experience aversive. These differences in pharmacodynamic response to the drug all have a significant genetic component, and at the behavioral level are a starting point for choice of contexts and likelihood that context influences will play a significant role. The more general point is that there is also heterogeneity of course for alcohol-specific risk from early on in the drinking career.

Multiple Pathways of Alcohol-Specific Risk: Heterogeneity of Course of Problem Use

Just as there are multiple developmental pathways of nonspecific risk, parallel evidence for heterogeneity of course for alcohol-specific risk has also been found both for problem use and also for disorder. We first describe findings from the Arizona Family Study (Chassin, Barrera, Bech, & Kossak-Fuller, 1993), one of the core studies that has demonstrated heterogeneity in trajectory of precursive alcohol problems, which in turn lead into disorder. The Chassin study utilizes a high risk sample of COAs and controls. Its trajectory analyses used one of the most common problem drinking indicators, binge drinking (5 or more drinks in a row), and tracked the longitudinal course of problem use across the 12 to 23 age range. This is the age period between the very earliest-start drinking and the time where downward tapering of heavy drinking begins for the majority of drinkers—in the early to mid-20s (Chassin, Pitts, & Prost, 2002). Four trajectories of binge drinking were identified that differed in acceleration into problem use as well as maximum level of bingeing (Figure 18.10). The heaviest/highest problem users only involve about 20% subjects—even in this high-risk sample—and reach their peak use substantially earlier than the other heavy-use

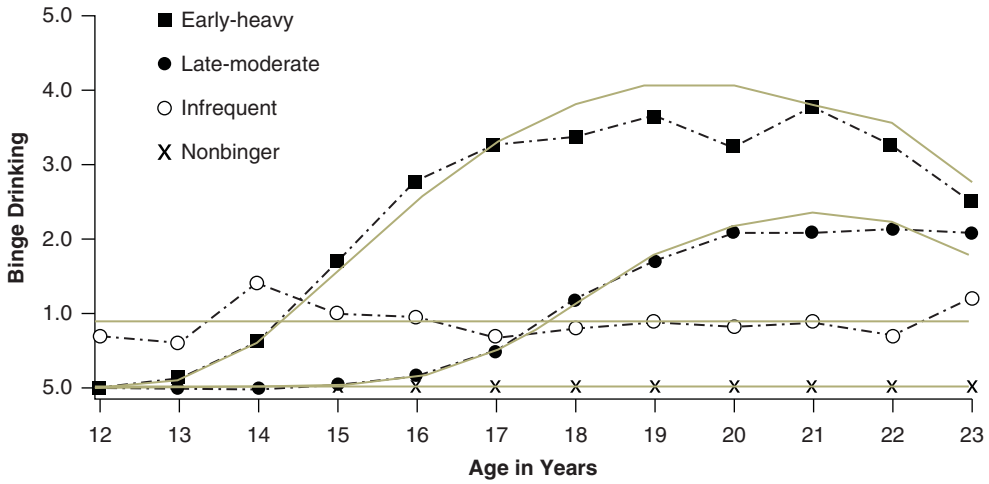


Figure 18.10 Growth curve trajectories of binge drinking from adolescence through emerging adulthood. Note: solid lines represent estimated growth trajectories for the three groups from the mixture modeling. Dashed lines represent observed means of binge drinking at each age for each group. Observed frequencies of binge drinking (past year) ranged from 0 (none) to 5 (1–2 times a week). Nonbinger group, $N = 176$, 39.5% of the sample. Early–heavy group, $N = 93$, 20.9% of the sample. Late–moderate group, $N = 134$, 30.0% of the sample. Infrequent group, $N = 43$, 9.6% of the sample. See footnote 1. *Source:* Reproduced from L. Chassin, S. C. Pitts, & J. Prost, Binge drinking trajectories from adolescence to emerging adulthood in a high-risk sample: Predictors and substance abuse outcomes, *Journal of Consulting and Clinical Psychology*, *70*(1), 72, Figure 1, 2002. doi:10.1037/0022–006X.70.1.67

group, the late-moderate bingers. Two groups show little (infrequent binger) to no problem (nonbinger) use. More involvement with drinking peers was either causal, or traveling with the heavy consumption patterns (adolescents with greater peer drinking were more likely to be in the heavier drinking groups, and the heavy-early group had the highest levels of precursive risk (alcoholic family membership, parent with antisocial personality disorder, and males were highest in externalizing behavior at baseline). Females were more likely to be in the nonbinger and infrequent groups. Perhaps most importantly for the linkage of earlier problem behavior to later problem outcome, all the bingeing groups were at higher risk for later substance use disorder. Equally importantly, speaking to the issue of early harbingers foreshadowing later problem outcomes, even the lowest frequency bingers (infrequent group) were as likely as the early–heavy group to develop drug abuse and dependence. In contrast, those without adolescent binge drinking were thereafter most likely to become full-time college students.

The Chassin group findings have been largely duplicated by nonhigh risk and general population studies examining trajectory variations from adolescence into early adulthood (Schulenberg, O'Malley, Bachman, Wadsworth, & Johnston, l996a; Windle, Mun, & Windle, 2005), as well as by studies beginning in later childhood (Hill, White, Chung, Hawkins, & Catalano, 2000). This work also has documented the importance of both precursive nonalcohol behavioral differences and context (peer drinking) as differentiators of class membership. Moreover, the Schulenberg et al. study demonstrates a point that is essential to our emphasis on the importance of understanding developmental heterogeneity, namely that the population trajectory (i.e., the summative trajectory for all individuals) is completely misleading as a characterization of developmental process for any of the individual trajectory groups; patterning conveyed by using population means does not summarize any subgroup of individual experiences.

One last point: in these studies, one problem use trajectory that systematically emerges is characterized by elevated child problems prior to adolescence and a damaged, high stress socialization environment, often enriched for family history of alcoholism. The Chassin Early-Heavy group trajectory, the Hill Early High trajectory, the Schulenberg Chronic group, and the Windle Very High Heavy Drinking trajectory group all fit this pattern. The residual trajectory class (or classes) identified have typically been less well replicated and the more recent and more precise analytic work gives some clues about why this might be. If more developmental variability exists in those lower risk, lower symptomatology subgroups, then less differentiating analyses will more often merge them, sometimes identifying them as one other group and sometimes identifying more than one.

Heterogeneity of Alcohol Use Disorder and Variations in Developmental Course of the Disorder/Phenotype

In contrast to the work on youth and early adulthood, efforts to characterize course in adulthood historically have had a more clinical focus, namely to describe differences in emergence and course of symptoms that would effectively differentiate subsets of patient populations with different clinical histories, current functioning, and longer term prognosis. In addition to their potential descriptive utility in sorting out the disparate symptomatology of alcohol use disorder, the underlying motivation for such typological classification is to identify subtypes of individuals who would respond differently to treatment regimens, and might also conceivably need different regimens for resolution of the disorder (Leggio, Kenna, Fenton, Bonefant, & Swift, 2009). To identify the subtype then provides a clinical shorthand that quickly conveys all of this information by means of a typological label.

Babor's (1996) still relevant historical review of the classification/typology literature has been able to identify these typological classifications as far back as 1850. His paper concludes that the major empirical classification studies repeatedly rediscover two types, summarized as Apollonian and Dionysian. The former is characterized by later onset of alcohol dependence, a slower disease course, fewer social complications, less psychological impairment and a better prognosis, and the latter is characterized by early onset, physical aggression, more severe symptomatology, a denser positive family history (suggesting a stronger genetic basis for the disorder), and more personality disturbance (Babor, 1996). At the same time, the simplicity leaves important features out, and the field has continued to struggle with how best to characterize these differences in clinical presentation and developmental course. The most recent summary review of this work by Leggio and colleagues (2009) identifies 12 classification typologies that characterize anywhere between two and five subtypes. From the perspective of these volumes, there are two problematic features of these classification systems that go relatively un-noticed. One is the heavy utilization of treatment samples to establish the classification scheme. This is inherently a biased activity, given the restrictions in range of variation, severity, comorbidity, and sometimes even age that are found in such clinical populations. Given

that only about 8% of those with alcohol use disorder receive treatment (Edlund, Booth, & Han, 2012), there is a broad swath of diagnosable cases that never come under scrutiny. Moreover, among those not under study are those who move into diagnosable problem, but then move out of it. The features of the disorder (and its surrounding context) that produce this are thus lost to the models of causal structure that are constructed to explain the course and variations of the disorder. At the same time, general population studies may not be heavily enough seeded with risk to allow disaggregation of rarer factors, or comorbidity that may be an intrinsic part of the disorder. Carefully selected patient samples and their cohorts (e.g., COGA) may allow investigators to address this issue, but the generalizability question needs to be kept in the forefront when doing so.

The other problematic issue is the lack of attention to full developmental course of the syndrome, and in particular, the identification of risk factors which are present prior to appearance of the clinical symptoms. In the process, these frequently nonspecific characteristics are missed and proximal causes are interpreted as critical because the distal structure is already in place. Newer studies using factor analytic and cluster analytic techniques (e.g., Moss, Chen, & Yi, 2010) have avoided the sampling bias issue by using population samples—the National Comorbidity Study (NCS) (Kessler et al., 1997) and its follow-up, and the more recent National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Hasin et al., 2007)) and follow-up (Dawson, Stinson, Chou, & Grant, 2008) for their analysis but they still are hindered by the developmental course issue since these studies start at age 18 and characterizations prior to that are assessed retrospectively. To address these issues, a developmentally focused conceptual analysis by the senior author led to a proposal for a four trajectory alternative to the two factor model (Zucker, 1987). It was based on epidemiologic studies that suggested there were differentiations in the life course trajectory of alcohol abuse and dependence as a function of comorbidity and life course environment. A developmentally filtered literature review of individual differences in adolescent heavy drinking patterns, their possible relationship to adult alcoholism, as well as data on the etiology of these earlier drinking patterns and their relationships to adult social adaptation outcome also contributed to the model. It consisted of three alcoholism trajectories that differed in the type of comorbidity they shared, and one alcohol-specific, noncomorbid trajectory, developmentally cumulative alcoholism (Zucker, 1987). Descriptions of course, including time of onset and extensiveness of course, were of special interest. Continued attention to the developmental issue of diagnostic continuity or discontinuity led in 1994 to a modification of the noncomorbid trajectory subtype that parsed it into three subtypes (Zucker, 1994; also see the lower half of Figure 18.11). Although the model was formulated two decades ago, prospective and retrospective studies continuing up to the present day, and covering a developmental span as far back as age 3 (Meier et al., 2013), and as far forward as 56 (Jacob, Koenig, Howell, Wood, & Haber, 2009), have repeatedly reaffirmed the core characteristics and trajectories of the subtypes (Windle & Scheidt, 2004; Jackson, O'Neill, & Sher, 2006; Jacob et al., 2005, 2009; Meier et al., 2013). At the same time, because of specific sample characteristics (life course span traversed by the study, sample-specific comorbidity characteristics), not all of the subtypes typically emerge from a single analysis. Because of the model's developmental utility, we briefly outline core elements of each of the subtypes. Table 18.2 shows the parallelism between model subtypes and the empirically derived subtypes from three of the most relevant prospective studies.

As noted, three of the types are characterized by way of their association with specific forms of psychiatric comorbidity and the three without the comorbidity are differentiated by timing and continuity/discontinuity of

TABLE 18.2 Parallelisms Between Longitudinal Subtype Typology and Prospective Trajectory Class Studies Traversing Early Childhood to Late Middle Adulthood[1]

	Jackson and Sher (2005)	Meier et al. (2013)	Jacob (2005, 2009)
Antisocial alcoholism	Chronic	Persistent	Severe chronic
Developmentally limited alcoholism	Developmentally limited	Developmentally limited	Young adult
Negative affect alcoholism	Later onset AUD	Adult onset AD	
The primary alcoholisms			
Isolated AUD	—	Age 26 AD	
Episodic alcoholism	—	Recovery AD	Severe nonchronic
Developmentally cumulative ALC	—	—	Late onset
Study age-range sample	18.5–29.5 High-risk college student (50% FH+)	3–32 General Population	15–56 Vietnam Era Twin Study with AD at least once

[1] *Notes:* ALC = Alcoholism; AUD = Alcohol Use Disorder; AD = Alcohol Dependence; FH+ = Family History Positive for Alcoholism.

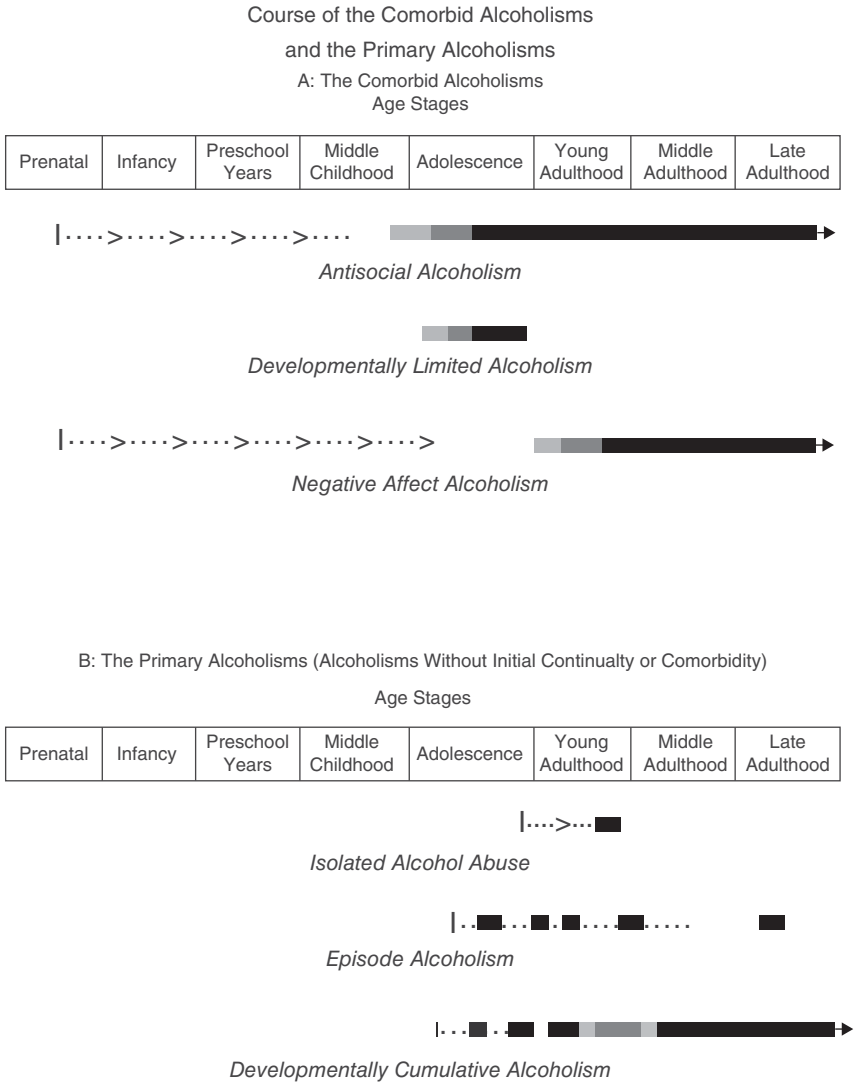


Figure 18.11 Course of the comorbid alcoholisms and the primary alcoholisms.

AUD symptomatology. The first of the comorbid forms, the one most commonly described in the literature, is the antisocial type. This trajectory has already been described heavily in the adolescent problem behavior literature but it had not been given a clinical label by researchers (Maggs & Schulenberg, 2005; Weber, Graham, Hansen, Flay, & Anderson, 1989) until very recently, when it has alternately been described as an undercontrol pathway (Zucker, Heitzeg, & Nigg, 2011); a behavioral disinhibition pathway (Iacono, Malone, & McGue, 2008), and an impulsivity pathway (Dick et al., 2010). This is Babor's Dionysian type, also Cloninger's (1987) male-limited (type II) group, and involves a continuity pathway, a co-association of long standing between alcohol problems and antisocial behavior in its developmentally progressing forms (Hussong, Curran, Moffitt, Caspi, & Carrig, 2004; Zucker, Ellis, Bingham, & Fitzgerald, 1996a). The antisocial behavior first shows as conduct problems, later emerges into delinquent activity, and ultimately shows as antisocial personality disorder. This progression is driven by genetic diathesis (Cloninger, 1987), and is nurtured not only by a dense family presence of heavy alcohol use, but also by contact with delinquent and heavy substance using peers, poor parental monitoring, and neighborhood residential instability. The antisociality plays a central part in the emergence of the alcoholism, and in turn, the alcohol problems and alcoholism are an essential piece in the emergence of the antisocial adaptation (see Zucker et al., 1996a) for a fuller description of this type). Prospective studies by Buu, Hussong, and Mayzer and their colleagues

(Buu et al., 2009; Hussong, et al., 2007; Mayzer, Fitzgerald, & Zucker, 2009) describe how this pathway emerges in earlier life, and studies by Windle & Scheidt (2004), Jackson & Sher (2005), Meier et al. (2013) and Jacob et al. (2009) describe the process from early to later adulthood.

A second type, developmentally limited alcoholism, likewise involves a comorbid antisocial connection, but the antisociality is stage limited (i.e., this is the stage specific delinquent and impulsive activity of the adolescent problem behavior syndrome (cf. Donovan & Jessor, l985; Moffitt & Walsh, 2003). The antisociality is coupled with the problem alcohol use endemic to adolescence. Equally importantly, this age-stage is one where cortical and neurohormonal systems are changing, and in the process affect decision making and goal setting, including making judgments about alcohol, sex, sensation seeking, that are often in conflict with the social structural need to develop the cognitive skills necessary for the transition to adulthood (Brown et al., 2008; Windle et al., 2008). Howard Blane (1979) called attention to the effects of these processes on heavy drinking more than a generation ago, without giving it a formal alcoholism label (he called it frequent heavy drinking), but the trajectory of alcohol use it embodies continually is documented in the prospective literature (Table 18.2; also see Schulenberg et al., 1996a, regarding the Decreasing Binge Drinking trajectory). It drops off with cortical and neurohormonal maturation, and with the onset of the role demands and responsibilities of adulthood.

The third type begins with the emergence in childhood and adolescence of internalizing symptomatology, a phenomenon that is more likely to occur in high risk populations such as alcoholic families, where negative emotionality, family conflict, and stress are more evident (Colder & Chassin, 1993; Hussong, et al., 2008; Rolf, Johnson, Israel, Baldwin & Chandra, l988), and also where independently, the high levels of adult alcohol use provide a context in which heavier drinking is much more likely to be present. This in turn drives the progression into a trajectory of severe, and sustained alcohol related problems. This pattern, termed negative affect alcoholism, was historically seen as more common among women; more recent work qualifies that view, with the qualifier that the negative affect-heavy alcohol use linkage is restricted to women who are already problem drinkers. Under emotional stress, nonproblem-drinking women are more likely to experience depression and anxiety but not increase their consumption (Chaplin, Hong, Bergquist, & Sinha, 2008); but for already heavier drinking women, negative mood arousal produces stronger urges to drink (Rubonis et al., 1994). An earlier study by Olenick and Chalmers (1991), reported a similar finding. Women in treatment for AUD reported use of alcohol to alter negative mood 4 times as often as did women who were social drinkers. The differences for men were also present, but were significantly less powerful (the ratio was 2:1). The more general point is that even though the circumstances for high negative affectivity are present, the learning about heavy drinking as a vehicle for anxiety reduction needs to take place before the negative affect-alcohol use link will be joined.

In contrast to the comorbid subtypes, the noncomorbid trajectories schematically presented in Figure 18.11 depict a set of alcoholisms that have no demarcated childhood antecedents. They involve sustained alcohol intake, which leads to severe, alcohol related symptomatology of varying durations. No *diagnostic* comorbidity is known to have linkages to their onset, and they are identifiable more by their drinking related consequences than their nondrinking etiology. This is the type that is most often viewed as the pure example of alcoholism as an addictive disorder. It is driven by alcohol-specific vulnerabilities, including a lower sensitivity to ethanol's intoxicating effects (Schuckit, Smith & Tipp, 1997; Schuckit et al., 2001) and a greater subjective experience of activation and energy that makes consumption both more reinforcing and less aversive (Newlin & Thompson, 1990). Hill, Steinhauer, Locke-Wellman, and Ulrich (2009) proposed that a central neural vulnerability endophenotype drives the progression, but the unusual nature of her sample makes it unclear about the extent to which her findings are more generally applicable to the high-risk population of noncomorbid COAs. A second, not necessarily mutually exclusive hypothesis is that this trajectory and its other more truncated noncomorbid forms is driven by elevated environmental stress occurring in very high use social contexts that provides a support and value structure for alcohol as the drug of choice for tension reduction. Under circumstances of more time-limited stress (e.g., immediately preceding or following the breakup of a marriage), isolated abuse may occur (Leonard & Rothbard, 1999). Under circumstances where the stress is recurring (e.g., times of heightened stress related to periodic job layoffs (cf. Catalano, Dooley, Wilson, Hough, 1993; Mulia, Zemore, Murphy, Liu, and Catalano, 2013), or for those in intermittently high stress occupations, the symptomatology becomes episodic. For those whose contextual and individual vulnerability match is greatest, the alcohol seeking behavior eventually moves into a chronic adaptation. This latter trajectory has been termed developmentally cumulative alcoholism.

There are obvious parallels between these latter three trajectories and the developmentally limited but antisocially comorbid pattern of adolescence. Although the form of all four of these types is similar, for the developmentally limited pattern, individual level etiologic risk factors have already been identified, but the onset and termination of the disorder is driven by nonindividual level contextual factors, to which the individual responds. Nonresponsivity (i.e., the perseverance of the high consumption level in the face of increasing social stigma and penalty), is what differentiates the developmentally cumulative pattern from both the developmentally limited and the episodic pattern. This may also be the case for the isolated abuse variant, and in fact both Schuckit and Moos and their colleagues have specifically addressed this issue (Moos, Brennan, & Schutte, l998; Schuckit, l988). However, the longitudinal structure of these variants has been less well charted.

THE GENETICS OF ALCOHOL USE, PROBLEMS, AND AUD

Alcoholism as a Genetic Disorder

Alcoholism is a complex phenotype and the previous two sections on heterogeneity of risk and disorder drive this point home. The fact that the phenotype's expression is dependent upon the presence of an environmental object (ethanol) would suggest environmental factors play a significant role in etiology, but the evidence for a genetic contribution to alcoholism risk is also indisputable. Evidence from family, adoption, twin, and cross-fostering studies all support this conclusion. Twin studies consistently find that genetic influences account for approximately 45% of the variance of AUD and measures of quantity and frequency in adulthood with little or no shared environmental effects (Dick et al., 2009). The relative genetic and environmental influences are moderated by age however, and initiation of alcohol use exhibits both moderate genetic and shared environmental influences, as does quantity/frequency and AUD, in adolescence (Rhee et al., 2003; Dick et al., 2009). Further, longitudinal studies have found that genetic influences increase and shared environmental influences decrease with age for alcohol use and externalizing phenotypes more generally (Bergen et al., 2007). This suggests that shared environmental influences are important to initiation and early drinking, but that both genetic and nonshared environmental influences (i.e., environmental influences that contribute to differences among relatives) are determinative for long term problematic alcohol use that persists into adulthood.

Several multivariate twin studies of substance use phenotypes have also established that there is substantial common variance in genetic influences among AUD, nicotine dependence, and illicit drug dependence, as well as with their precursive nonspecific risk components, namely antisocial behavior and disinhibited personality traits (Button et al., 2006; Kendler et al., 2007; Slutske et al., 1998, 2002). Family transmission studies have also found that the transmission of a general externalizing factor best accounts for parent–child similarity for AUD, other substance use disorders, and antisocial behavior (Hicks et al., 2004). That is, rather than disorder specific risk, parents pass on a general behavioral disinhibition liability to the next generation that then increases risk for multiple externalizing disorders. A recent combined twin, adoption, and family study further demonstrated that this general parent–child transmission was primarily genetic (Hicks et al., 2013).

The findings of genetic overlap among antisocial behavior and substance use disorders prompted researchers to fit biometric factor models to estimate the heritability of the externalizing factor to estimate the extent to which their comorbidity was due to common genetic and environmental influences. These studies found that externalizing is highly heritable (70–85%) in late adolescence and young adulthood, with little or no shared environmental influences (Kendler et al., 2003; Krueger et al., 2002). These estimates are typically higher than for any individual disorder, with the externalizing factor accounting for the majority of genetic variance in each disorder. Each substance use disorder, however, also exhibits specific genetic and nonshared environmental variance. These findings are consistent with a hierarchical model of risk, involving a highly heritable nonspecific risk factor, but with the final phenotypic expression of the nonspecific risk determined by environmental and genetic influences that are unique to each phenotype.

The importance of the general externalizing factor in the emergence of symptoms of substance use disorders appears to be moderated by age, peaking in late adolescence and declining thereafter as disorder-specific effects increase (Vrieze et al., 2012). Most of the decline is attributable to externalizing accounting for less heritable variance in the individual disorders, while disorder-specific genetic and environmental effects increase with age. These findings are consistent with the interpretation that a highly heritable behavioral disinhibition liability leads to nonspecific substance use and antisocial behavior in late adolescence, but that substance specific risk factors increase in importance as people age, leading to greater specialization in substance use and the maintenance of chronic problem use.

It is important to note that variation in heritability effects either for externalizing or for alcohol problems per se is not evidence indicating weakness of a heritable effect. Rather, a characteristic of complex phenotypes such as alcoholism is that the variability in estimation is both a function of the way the phenotype (such as diagnosis) is measured, as well as the variability in the population. In turn, the population variability is itself a function of environmental exposure (e.g., alcohol availability), age structure, and population genetic variations.

Another important point is that alcohol use phenotypes are likely to vary in their genetic architecture. Even the symptoms that constituted the *DSM-IV* diagnostic categories of alcohol dependence and alcohol abuse are not unequivocally the same phenotype; that is, they may not just be indicators that differentiate severity but rather be differentiable phenotypes. This is the evidence that drove the development of the typology outlined in the previous section. Epidemiologic data support this view of multiplicity of phenotypes; approximately a third of the alcohol dependence population does not also meet criteria for abuse (Hasin & Grant, 2004). In other words, one may have physiological dependence without ever having gone through an abuse phase. Further, because alcohol is so widely available and frequency of use does not necessary result in dependence, the genetic and environmental influences on dimensional measures of quantity and frequency of use are likely to be at least somewhat distinct from those for symptoms indicative of pathological use. Evidence for this includes findings that heritability estimates for abuse and dependence tend to be greater than for measures of use (Hicks et al., 2011); this dialogue continues to remain an active one both in the genetic and the epidemiologic literature (Hasin & Grant, 2004; Ridenour et al., 2003). The issue of phenotype definition remains an essential one in attempting to identify risk genes and understand genetic influences on alcohol use and AUD.

In terms of specific genetic effects, the most robust genetic markers associated with alcohol use and AUD are variants involved in the metabolism of alcohol. The two candidate genes that protect against heavy drinking are the functional genetic variants of alcohol dehydrogenase that exhibit high alcohol oxidizing activity (ADH), and the genetic variant of aldehyde dehydrogenase (ALDH2) that exhibits low acetaldehyde oxidizing activity (Li, 2000). The ALDH2 variant is common in some Asian populations. Those who have it experience a flushing reaction, headache, palpitations, dizziness, and nausea after consuming alcohol. The aversive experience appears to be protective in the populations where that variant exists (Thomasson, Crabb, Eadenberg & Li., 1993). However, the low prevalence of the ALDH2 deficiency in individuals of European and African ancestry results in very low explanatory power for the U.S. population. High ADH activity is associated with a similarly unpleasant set of symptoms following drinking; here the genetic variants involving the ADH2*2 and ADH3*1 alleles appear to be protective (Thomasson et al., 1993). At the same time, consistent with a complex genetic model, a cross-national study by Reich and Li (1994) observed that even though Koreans have a relatively high rate of ALDH2 deficiency, alcoholism rates are very high in this population, indicating that cultural influences may override the impact of the biological feedback system (see the discussion of cross-domain relationships in Section III).

Beyond the genetic variants involved in alcohol metabolism pathways, a number of candidate genes have been identified that may contribute to etiology, but studies are not uniformly confirmatory either of a link to alcoholism or to some intermediary trait such as externalizing or internalizing behavior. Furthermore, there is little understanding of any underlying mechanisms, although currently a number of teams are aggressively pursuing this problem. For example, variants of genes in the serotoninergic (e.g., 5-HTTLPR), dopaminergic (e.g., DRD2), and monoamine oxidase A (MAO A promoter) have at times been associated with alcoholism or phenotypes associated with alcoholism, but the literature includes as many negative results as positive findings. Perhaps the most promising candidate gene thus far is the previously mentioned GABRA2. GABA is a major inhibitory neurotransmitter that is sensitive to ethanol including its anxiolytic effects (Grobin, Matthews, Devaud, & Morrow, 1998). GABRA2 has now been associated with several externalizing phenotypes including alcohol and drug dependence, antisocial personality disorder and conduct disorder, and an electrophysiological endophenotype (Dick, 2007). Also, as already noted in the section on nonspecific risk, the effects of GABRA2 may be moderated by environmental context, in particular parent monitoring (Dick et al., 2009; Trucco et al., 2015).

While sorting through the findings for candidate genes remains an ongoing task, recent advances in high-throughput genotyping technology have resulted in a sea change in gene association studies for complex phenotypes. Rather than focus on specific genes or potential regions of interest in linkage studies, these new genotyping technologies include markers that effectively cover the majority of the human genome. The most popular of this type is the genome-wide association study

(GWAS), and entails genotyping individuals on more than 1 million single nucleotide polymorphisms (SNPs). SNPs are not the only form of genetic variation, but have been of primary interest because they are a simple form of genetic variation that can be efficiently genotyped. Also, the fact that most SNPs are common fits with the common variant common disease hypothesis, that posits that the heritable basis of common diseases or disorders are likely a function of relatively common forms of genetic variation, has also made them of significant interest. Evaluations differ as to the scientific yield from GWAS (Visscher, Brown, McCarthy, & Yang, 2012). On one hand, GWAS have identified thousands of variants for dozens of traits and disorders. On the other hand, the biological significance of many of these SNPs is unclear, and virtually none of these hits have what would traditionally be considered even a medium sized effect (odds ratio > 1.30 for minor allele); even SNPs that exceed genome-wide significance tend to have a small (odds ratio 1.10 to 1.20 for minor allele) to very small effect (odds ration < 1.10 for minor allele).

The results of GWAS for alcohol use phenotypes have been relatively sparse. An early GWAS study of alcohol dependence included over 1,500 male cases and 2,300 matched controls detected two SNPs on chromosome 2 in linkage disequilibrium with the peroxisomal trans-2-enoyl-coengzyme A reductase (PECR) gene, which is involved in fatty acid metabolism and primarily expressed in the liver (Treutlein et al., 2009). A much larger study of alcohol consumption detected an association with the autism susceptibility candidate 2 gene (AUTS2) in a discovery sample of 26,317 individuals that was replicated in a sample of 21,185 (Schumann et al., 2011). The mechanism by which AUTS2 effects alcohol consumption is unclear, but it has been linked with other neurobehavioral disorders in humans and alcohol sensitivity in animals. Notably, this study failed to detect an association with the PECR gene. Several other GWAS have failed to detect any genome-wide significant SNPs. Equally importantly, no previously studied candidate genes have been identified in a GWAS. New consortium efforts are underway for both alcohol consumption and AUD with the hope that old and new efforts will eventually be combined to form the mega-samples needed to identify the subset of SNPs that account for the majority of common genetic variation contributing to alcohol use and AUD.

A more likely scenario is that understanding the genetics of complex behavioral phenotypes such as alcohol use and AUD will require delineating the interplay between genetic and environmental influences. A potentially viable strategy is that if SNPs can be identified via large consortia, smaller studies with denser assessments such that include longitudinal measures of alcohol use phenotypes and the environmental context can use the leads from GWAS to delineate the interplay among genetic and environmental influences over the course of development. Also, the pathway from genetic variation to complex phenotype is almost certainly indirect involving a multilevel, multistage, process. Links in some of these stages may not be detectable at the behavioral level. As such, delineating the mechanisms of risk will likely involve the kind of multidisciplinary approach we have described here, which involves piecing together lines of evidence from disparate methods to gain a greater understanding of the multilevel processes that are likely at work.

Gene–Environment Interplay

The foregoing not only illustrates the importance of both genetic and environmental influences on the development of AUD, but also suggests that the underlying mechanisms of risk are a function of gene–environment interplay rather than simply main effects of genes and environments. Two mechanisms of gene–environment interplay are gene–environment (GxE) correlation and gene x environment (GxE) interaction. GxE correlation refers to the nonindependence between a person's genotype and the likelihood of exposure to environmental risk, such that those with higher genetic risk also tend to experience greater environmental risk exposure (Scarr & McCartney, 1983).

Passive GxE correlations arise from parents providing both the genes and the rearing environments; hence parental AUD will also confer risk for exposure to a higher risk rearing environment. For example, Buu et al. (2007) tracked the residential migration patterns of families with and without an alcoholic father over a 12-year period. Families with an alcoholic father were more likely to either remain in or move to a more disadvantaged neighborhood (high crime, poverty, and residential instability). As a consequence, these neighborhood characteristics predicted more symptoms of alcohol, nicotine, and marijuana dependence in the offspring of these men, as well as more symptoms of antisocial personality disorder and major depression in young adulthood (Buu et al., 2009).

As children transition into adolescence and gain greater autonomy in selecting their environments, active GxE correlations become more relevant mechanisms in the development of substance use and abuse, which also emerge during the same developmental interval (Bergen et al., 2007; Scarr & McCartney, 1983). Active GxE correlations primarily arise because heritable traits increase

exposure to trait-friendly environments that then increase risk for substance use disorders. Using a longitudinal twin study, Hicks et al. (2013) found that the socialization trait construct (willingness to follow rules, accept adult supervision, and endorsement of conventional values) predicted exposure to high-risk environments (deviant peers, parent–relationship problems, academic difficulties, stressful life events) in middle adolescence, even after controlling for stability in the child's environmental context from childhood to adolescence. In turn, high-risk environments in middle adolescence mediated some—but not all—of the association between childhood socialization and substance use problems in late adolescence. Results of biometric modeling revealed that 78% of the genetic overlap between childhood socialization and substance use problems in late adolescence was accounted for by the heritable variance in the environmental measures assessed in middle adolescence. That is, to the extent that childhood socialization accounted for heritable risk in substance use problems, the mechanism was mostly indirect, via increased exposure to high-risk environments.

GxE interactions have also been documented for alcohol use and AUD, and also emphasize that the importance of genetic influences on alcohol use outcomes varies as a function of the environmental context. For example, in a Finnish study, Rose and colleagues showed that genetic influences on adolescent alcohol use were stronger in urban areas while shared environmental influences were stronger in rural areas. Later work by the same group (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001) extended these findings by demonstrating similar patterns of GxE interaction for areas with more young adults, greater migration, and higher regional alcohol sales. Other investigators have found that genetic influences on alcohol initiation and alcohol use were weaker for adolescents who were highly religious (Koopmans, Slutske, van Baal, & Boomsma, 1999) and for women who were married (Heath, Jardine, & Martin, 1989), respectively. A common thread that may be operating across these environments is one of greater social control, such that more constrained environments depress the influence of genetic factors. Such an effect is not limited to alcohol; for example, genetic influences on smoking are attenuated in the context of high parental monitoring (Dick et al., 2007). Hicks et al. (2009) provided a comprehensive test of this hypothesis by examining the impact of six different environmental variables on the genetic influence of a composite of externalizing disorders in late adolescence. For each environmental variable, genetic influences on externalizing were greatest in the context of greater environmental adversity. These findings are consistent with a conceptualization that there is a general mechanism of gene–environment interplay for externalizing disorders such that those with the greatest genetic risk are the mostly likely both to be exposed to environmental risk (GxE correlation) and to be most sensitive to the influences of environmental risk factors (GxE interaction).

Gene–Brain–Environment: The Site of Gene–Environment Relationships

These twin studies provide clues to the interplay between the aggregate effect of genes and broad environmental influences. To uncover more mechanistic processes, however, will require delineating how the effects of specific genes are expressed in brain, and how the influence of these genes on more proximal processes (e.g., greater sensitivity to alcohol cues or consumption) contribute to alcohol use problems.

In contrast to GWAS, some researchers take a hypothesis driven approach that entails a three part strategy of genotype to brain to alcohol use phenotype. These approaches do not attempt to link the gene to AUD, but rather to intermediary processes that may contribute to risk for AUD including reactivity to alcohol-related stimuli (e.g., alcohol cue reactivity). Hutchison et al. (2008) reported a multi-outcome investigation of the cannabinoid receptor 1 (*CNR1*) gene and AUD, focusing on effects for individuals with at least one C allele in SNP rs2023239. *CNR1* codes for the cannabinoid receptor type 1 (CB1) that is densely localized in brain regions associated with drug-seeking behavior including the ventral tegmental area, nucleus accumbens, prefrontal cortex, basolateral amygdala, and hippocampus. Among the many findings, post mortem analyses of human prefrontal cortex revealed greater levels for individuals with the C allele. Further, the C allele was associated with greater activation in the midbrain and prefrontal cortex elicited in an alcohol cue paradigm, greater subjective reward when drinking alcohol, and more positive outcomes after treatment with a medication (olanzapine) that targets the mesocorticolimbic neurocircuitry. In a similar study, Ray et al. (2013) investigated links between variants of the mu-opioid receptor (OPRM1) gene, neurological reactivity to an alcohol taste cues task, and alcohol use among individuals with AUD. Relative to A-allele homozygotes, carriers of the G-allele of the OPRM1 exhibited greater insula and orbitofrontal cortex activation and had stronger negative fronto-striatal functional connectivity for ventral and dorsal striatal regions when viewing alcohol versus water cues.

These studies are but two examples of a translational approach of investigating genetic risk for AUD along with neuroscience. One is that genetic variation to phenotype is almost always indirect, involving a multistage process. These stages often include genetic variation, motivational (reward), appetitive (drug sensitivity, craving), cognitive (expectancy) mechanisms, and facilitating or dampening environmental effects. Additionally, variables in these processes may only account for small amounts of variance in the clinical outcome making their detection difficult at the behavioral level. Finally, the transcriptional role of genes that codes for the structure and function of neurons is sensitive environmental inputs, and variables such as stress, learning, and social interaction impact neurological development. Thus, the brain is the playing field within which gene–environment interplay ultimately takes place.

INTERMEDIATE-LEVEL ETIOLOGY IN BRAIN

The Core Neural Model of Addiction

The most prominent and dominant conceptualization of the core nature of drug addiction over the past generation has been that it is a disorder of the brain, a product of the long term interaction of drugs upon neural circuitry that produces compulsive drug seeking and use, even in the face of negative health and social consequences (Leshner, 1997). Although social context and behavior are clearly a part of the clinical syndrome, they are seen as consequences rather than essential parts of the causal matrix. The addictive process at the behavioral level begins with reward seeking that is initially framed as seductive and hedonic. Continued pursuit of the hedonic end state through increasing use leads to diminution of effect. This in turn leads to heightened reward seeking, but simultaneously leads to a dampening of reward response and increases in stress and anxiety, culminating in withdrawal if use is not sustained. Thereafter, use is negatively motivated, since its primary goal is to ward off the negative effects.

Although we have described this as an affective and behavioral sequence, the neurophysiological model undergirding the behavior is seen as the core mechanistic structure of the disorder. It initially involves the mesocorticolimbic dopamine system, including the nucleus accumbens, amygdala, hippocampus and prefrontal cortex, as the system where the pharmacological actions of ethanol converge to produce their reinforcing effects (see review in Weiss & Porrino, 2002). This system is critical to reward processing and centrally involved in the reinforcing properties of drugs of abuse (Robinson & Berridge, 2000) and is also modified by drugs of abuse (Volkow & Li, 2004). It is proposed that with repeated alcohol use, a loss of function occurs in this dopaminergic reward system, which results in a loss of motivation for natural rewards (Koob, 2013). This effect is further exacerbated by concomitant neural alterations in the brain stress system, mediated by corticotropin-releasing factor (CRF) in the extended amygdala and hypothalamic-pituitary-adrenal (HPA) axis, which lead to aversive, anxiety-like states. A combination of these effects results in the development of negative affect. As the negative affect increases, one sees compulsive use to avoid the negative affect effects (Koob, 2013). The end result is that addictive use hijacks both the brain's reward and stress response systems, in a compulsive cycle of use, stress, negative affective experience (withdrawal), repeated use to dampen the negative affect. An additional critical feature is that drug use disrupts the frontal cortical circuits that regulate motivation, drive, and self-control and changes in the memory circuitry increase the motivational salience of the drug and drug-associated stimuli (Volkow & Li, 2004). Some caveats are typically attached to this characterization, namely that exposure to conditioned cues (social contexts of use) can be a major factor in both causing and rearousing drug craving. However, the underlying structure of the disorder is conceptualized as a neural disorder involving fundamental and largely irreversible changes in circuitry.

Domains of Vulnerability

This account of the development of addictive disorder is dynamic, but it is not developmental. It describes the unfolding of a sequence of processes, which culminate in compulsive use and negative affect. Other work, both in parallel to the studies just described, and following from it, has taken a more straightforwardly developmental perspective by framing the question whether any of these sites of action has precursive/predispositional vulnerability, which would make the likelihood of both impairment of circuitry and alcohol seeking behavior more likely.

Both clinical and preclinical evidence suggests that the mesocorticolimbic dopamine system plays a role in preexisting vulnerability to addiction (McBride & Li, 1998; Volkow, Wang, Telang, et al., 2007), and variability in dopamine signaling has been associated in animal models with impulsive behavior more generally (Dalley, Mar, Economidou, & Robbins, 2008). Findings in substance dependent populations (e.g., Volkow, Wang, Telang, et al., 2007) also suggest a common pathway for vulnerability to impulsive behavior and addiction, involving variability in

mesocorticolimbic dopaminergic function, although all of this work is suggestive, given that it has been carried out on already addicted individuals.

At the neurocognitive level, executive functioning has also been identified as a significant precursive factor in the emergence of risk, which is in place prior to any impairment from use of addictive substances. Executive functioning entails the ability to regulate behavior to context and to maintain a goal set (Miyake et al., 2000). This is a multicomponential system, including response suppression/inhibition (the ability to strategically suppress a prepotent or prepared motor response), working memory (itself multicomponential), set shifting, and interference control (Pennington & Ozonoff, 1996). To the extent these capacities translate directly to behavioral differences, they have relevance to a spectrum of activities that elevate or dampen risk. They relate to wisdom in choice of peers, understanding of the importance of context to appropriate drinking behavior, ability to desist when encouraged to drink or encouraged to continue drinking under circumstances that indicate drinking consequences (such as increasing intoxication or the ability to get to work/school the next day and function adequately) may be costly in the long term. Extensive theory has linked aspects of executive control with alcoholism risk (e.g., Tarter, Alterman, & Edwards, 1985). However, data to support that link are mixed (e.g., Finn et al., 2002) and some evidence suggests that the risk element is primarily related to response inhibition (Nigg et al., 2006) more specifically, rather than to a general vulnerability from the broader executive control system. This issue remains to be settled.

In attempting to systematize this work, theorists have conceptualized these operating structures as two core psychological systems with neural underpinning, which are in dynamic tension and modulate one another (Eisenberg et al., 1997; Rothbart & Bates, 2006; Nigg, 2000; Zucker, Heitzeg, & Nigg, 2011). One is an effortful control system (Rothbart & Bates, 2006) involved in the control of behavior and attention in the service of goals that are distal in time and represented in memory or working memory rather than by immediate incentives and cues. Effortful control reflects activation in prefrontal cortex, likely corresponding with suppression of activity in subcortical regions (particularly the nucleus accumbens and amygdala) and is largely regarded as a top-down system.

The second system is the relatively automatic incentive reactivity system, which operates rapidly, responding to novelty or incentive cues for potential near-term reward or loss by interrupting behavior. The neural process is subcortical signaling of novelty (e.g., from the nucleus accumbens or amygdala), and is heuristically seen as a bottom-up process in the brain. An emerging literature suggests there may be dysregulation in both of these systems in at-risk populations prior to the onset of problem alcohol use (e.g., Heitzeg, Nigg, Yau, Zucker, & Zubieta, 2010; Yau et al., 2012). As part of the process, top down and bottom up responses mutually influence one another (Nigg, 2000; Rothbart & Bates, 2006); thus, incentive response also involves decision making (in the context of potential reward or loss).

In addition to the operation of these specialized domains of neural function, it has recently become appreciated that brain regions with synchronized behavior, while at rest, are functionally linked, thus forming resting-state networks (Salvador, Suckling, Schwarzbauer, & Bullmore, 2005). Resting-state functional connectivity MRI investigates these network linkages, operating in the absence of an externally cued task. A number of distinct networks have been described, including a salience network and an executive control network (Seeley et al., 2007), roughly mapping onto incentive reactivity and effortful control systems respectively. Recent evidence suggests that addiction and related phenotypes, such as risk-taking, are associated with coherence within and between these salience and control networks (e.g., Liu et al., 2009; Park et al., 2010). Of particular relevance is the finding of impaired connectivity between the striatum and prefrontal cortex in alcoholics, which was related to impairments in reward-guided decision making as well as an inability to control drug-craving (Park et al., 2010). This adds to the extensive data suggesting that at both the behavioral and neural level substance use problems are associated with a dysregulation of decision-making in the context of incentives; specifically, the subcortical, involuntary elements (limbic and striatal circuitry) are overresponding to salient drug-associated stimuli and cortical control (via frontal circuitry) over this response is impaired or inhibited, leading to more drug use and the maintenance of—and failure to exit from—a use pattern (Jentsch & Taylor, 1999).

The Genetics of Neural Individual Differences

To improve our understanding of the neurobiological mechanisms underlying risk for SUD, recent efforts have focused on identifying genetic factors that determine interindividual variability in dopamine signaling and its impact on the reactivity of effortful control and incentive reactivity systems. For example, variants in putatively functional genetic variants impacting the dopaminergic system (including DRD2 141 Ins/Del, COMT val^{158}met,

SLC6A3, DRD4 Exon III 48bp-repeat, and Taq1A) have been found to impact striatal reactivity to reward (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Forbes et al., 2009), prefrontal activation during inhibitory control (Filbey, Claus, Morgan, Forester, & Hutchison, 2012) and prefrontal connectivity (Tunbridge, Farrell, Harrison, & Mackay, 2013). Continued investigation of how altered dopamine signaling resulting from common functional genetic variation contributes to inter-individual variability in effortful control and incentive responding will aid in identifying detailed, mechanistic pathways by which functional genetic variation ultimately contributes to SUD.

Dynamic Changes in these Systems Over the Course of Adolescence

At the same developmental time during which a major buildup of alcohol use and alcohol problem behavior is taking place, concomitantly, neural alterations in control and incentive systems are occurring. The prefrontal cortex is one of the last brain regions to mature, with cortical pruning continuing into early adulthood (Gogtay et al., 2004). Progressive increases in the white matter of this region have also been shown during childhood and adolescence (Paus, 2005). These developmental changes directly influence behavioral regulation by enhancing signaling efficiency, improving signal:noise ratio, among other effects. Thus, throughout childhood, developmental gains occur in the ability to suppress or inhibit prepotent responses and the ability to suppress irrelevant information (Paus, 2005). Functional imaging studies have shown development of prefrontal control in cross-sectional studies showing adults have greater prefrontal activation when making risky decisions (Eshel, Nelson, Blair, Pine, & Ernst, 2007), responding to rewards (Galvan et al., 2006) and inhibiting motor responses (Rubia et al., 2000). Social and emotional skills are also developing throughout childhood and early adolescence (Kolb, Wilson, & Taylor, 1992), with associated changes in amygdala (K. M. Thomas et al., 2001) and prefrontal (Steinbeis, Bernhardt, & Singer, 2012) functioning.

The mesolimbic dopaminergic system also undergoes dramatic change during adolescence (Spear, 2011). Specifically, developmental alterations occur in the projections from dopamine neurons in the ventral tegmental area to subcortical regions including the dorsal striatum and nucleus accumbens, limbic regions including the amygdala and hippocampus and cortical regions, particularly the prefrontal cortex. The nucleus accumbens is of particular importance in this circuitry, as it is responsive to incentive stimuli and contributes to directing behavior by integrating affective, contextual, and goal-directed information via inputs from the amygdala, hippocampus and prefrontal cortex (Grace, Floresco, Goto, & Lodge, 2007). Adolescence is a time of increased reward seeking and risk taking, and it is believed that alterations in the responsivity of the nucleus accumbens to incentive stimuli may contribute to this behavior (e.g., Spear, 2011). Of major significance to the issue of developmental increases in alcohol use is evidence suggesting that the relatively early maturation of subcortical systems compared with prefrontal control systems may bias the motivation of adolescents toward seeking out immediate reward and associated impulsive, risky decision-making (Casey, Getz, & Galvan, 2008; Steinberg, 2010).

In parallel to this work, an emerging literature investigating the development of functional connectivity in the resting brain shows a progressive specialization into integrated functional networks across development, suggesting the maturation of more efficient neural pathways over time (e.g., Stevens, Pearlson, & Calhoun, 2009). Behaviorally, this may translate into more impulsive behavior in adolescents as these systems cohere at different time points, with incentive response systems consolidating prior to control systems (Casey et al., 2007). Furthermore, increased coherence between nucleus accumbens and prefrontal cortex from adolescence to early adulthood has been shown to be associated with decreases in risky decision making (Christakou, Brammer, & Rubia, 2011), suggesting a developmental significance of coherence *between* networks as well. This illustrates the dynamic complexity of brain–behavior relationships related to risky and impulsive behavior across development. How these mechanisms operate and interact needs to be more fully mapped to achieve a full explanation of the emergence and maintenance of individual risk. Given the high levels of substance involvement taking place during this age period, a detailed understanding of how the development of these systems relate to risky substance use is critical.

The developmental significance of these changes, when superimposed on a social structure that is encouraging the emergence of alcohol use, is major. From studies of adult animals it is known that repeated drug use has long-lasting consequences in the brain, including: down-regulation of tonic dopamine activity (Scafidi et al., 1996), which mediates incentive motivational states; sensitization of phasic dopamine firing to drugs of abuse (Jones, Marsden, & Robbins, 1990), which is linked to habit formation and is believed to underlie drug craving, or wanting and to be critically involved in the formation of

dependence (Robinson & Berridge, 2000); and suppression of the strength of developing functional connections between mesolimbic structures and the PFC (Thomas, Beurrier, Bonci, & Malenka, 2001), leading to compromised top-down executive control over behavior. Such effects are thus potentially being superimposed on this developing circuitry in adolescents who are drinking and the neuroplasticity of the adolescent period makes the brain particularly vulnerable to neurotoxic processes. Studies exploring the impact of alcohol on the mesolimbic dopamine pathway in *adolescent* animals find that ethanol exposure induces higher extracellular baseline levels of dopamine in adolescents, which continue into adulthood (Badanich, Maldonado, & Kirstein, 2007). This suggests long-term sensitization of the dopamine system, which may mediate vulnerability to later alcoholism (Guerri & Pascual, 2010). Furthermore, there is extensive evidence from animal models that the hippocampus and prefrontal cortex are particularly susceptible to the damaging effects of ethanol in adolescence (see review in Guerri & Pascual, 2010), with implications for incentive motivation through effects on learning and memory and top-down control over behavior.

Few studies have investigated the effect of alcohol on incentive and control processes in human adolescents but those existing studies are generally consistent with the animal findings. There is evidence in adolescents with AUD of increased activation to alcohol-related pictures in the incentive motivation circuitry, including amygdala and prefrontal cortex (Tapert et al., 2003). Studies of brain structure in human adolescent drinkers have also found reduced hippocampal volume (DeBellis et al., 2000; Nagel, Schweinsburg, Phan, & Tapert, 2005) and smaller prefrontal cortical and white matter volumes (DeBellis et al., 2005). In addition, functional studies in adolescent drinkers indicate abnormal activation patterns for several cognitive tasks involving these regions (e.g., Heitzeg et al., 2010; Schweinsburg, McQueeny, Nagel, Eyler, & Tapert, 2010; Tapert, Schweinsburg, et al., 2004), suggesting that alcohol consumption during adolescence may have lasting effects on the maturation of incentive and control circuitry. It is important to understand how this circuitry matures, by mapping changes in neural response patterns associated with both risk for alcohol problems and with actual use and its sequallae. The fact that adolescence is a time of heightened alcohol consumption makes this issue of great importance.

Several other issues have not yet been addressed in the work to date. These concern the relative importance of amount and timing of alcohol (and other drug exposure) in bringing about these changes, the degree to which other environmental exposures (e.g., stress) also play a role, and the degree to which early neurocognitive vulnerabilities (i.e., precursive risk) interact with the drug exposure in producing change. One domain where these changes may already have been behaviorally marked is at age of onset of first alcohol use. Earlier age at onset is associated with a more severe course of alcoholism, drug use disorder, poorer treatment response, and higher relapse rates (Grant & Dawson, 1997, McGue et al., 2001).

An understanding of these processes will require the kind of multilevel-multisystem explanatory structure advanced at the beginning of this chapter. A full explanation will benefit from careful neurobehavioral/neurocognitive characterization that takes into account key aspects of executive functioning, motivation, and selected associated systems such as social information processing, along with a characterization of the genetic profiles that create the greatest vulnerability, as well as the social contexts where vulnerability is most likely to develop unchecked. Given the developmental changes in neural circuitry during this interval, it is essential to characterize these effects developmentally. The creation of the cross-level, cross-time model we described early in this chapter was prompted by the need to characterize this dense matrix of risk pathways that was operating. At this point, we briefly illustrate the utility of the model, summarizing findings from the ongoing Michigan Longitudinal Study (Zucker, 2014) and collateral work from other groups that together define the multilevel interactive matrix of behavioral undercontrol, arguably the strongest nonspecific risk factor for alcohol problems and AUD (Dick et al., 2010; Zucker et al., 2011).

Figure 18.12 provides a map of this developmental matrix. The numbered pathways in the figure are those for which there is already evidence for connections. These pathway identifiers are inserted here in the text, along with citations from the work that provided the evidence for the relationship(s). The most well supported pathway is between behavioral undercontrol and problem alcohol and drug use. Extensive evidence exists for the cross sectional [19, 37], and also the prospective relationship [12, 28, 29] (see extensive reviews in Zucker et al., 2008, and Zucker et al., 2011). Relatedly, ventral striatal and medial prefrontal processing show up as important neural substrates involved in the control of behavior and emotion, with dysregulated functioning of these regions related to externalizing behavior problems [18] (Heitzeg et al., 2010). Furthermore, the functional connectivity of ventral striatum mediates the relationship between undercontrolled behavior and level of drinking [34, 35, 38] (Weiland

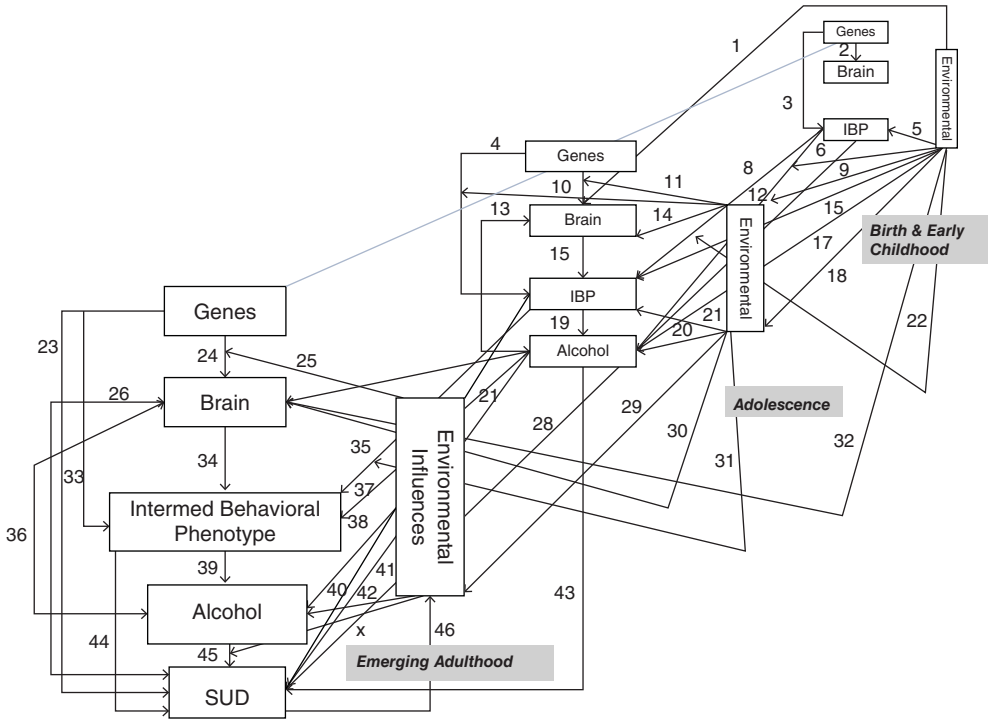


Figure 18.12 Cross-level mechanistic structure of undercontrol and related intermediate phenotypes. See footnote 1.

et al., 2012). Prefrontal control mechanisms in brain lose efficiency with alcohol use [38], which should exacerbate the development of these risky phenotypes [34] (Heitzeg et al., 2010). However, the evidence for this relationship is more indirect, and still requires some focused work to firmly establish it.

At the level of genetic influences, allelic variants of the serotonin transporter promoter polymorphism (5-HTTLPR), the corticotropin-releasing hormone receptor 1 (CRHR1), and a gene encoding the $GABA_A{}^{\alpha 2}$ receptor subunit (GABRA2) have differential effects on the phenotypic expression of undercontrol [2, 13, 36] (Twitchell et al., 2001; Trucco et al., 2015; Villafuerte et al., 2013) and negative emotionality (Glaser et al., 2014), and they also convey differential responsivity for the neural circuitry that regulates the phenotypic response [14, 24] (Glaser et al., 2014; Villafuerte et al., 2011).

Last, environmental moderation occurs at several levels of the behavioral risk pathway. Family conflict (Jester et al., 2005; Loukas, Fitzgerald, Zucker, & von Eye, 2001; Loukas, Zucker, Fitzgerald, & Krull, 2003), family cohesiveness (Jester et al. 2005), parental aggression (Fuller et al., 2003), parental distress (Loukas, Piejak, Bingham, Fitzgerald, & Zucker, 2001), and emotional support and intellectual stimulation from parents (Jester et al., 2005) all moderate the development of behavioral undercontrol [48, 49]. In addition, a more macrolevel influence, neighborhood residential instability, has effects on risk for development of problem alcohol and other drug use [9, 21, 32, 33] (Buu et al., 2007, 2009), and this in turn has long-term negative effects on where one ends up living (i.e., neighborhood quality effects) [50] (Buu et al., 2007), indicating a cascade effect from environment to problem alcohol use, back to environment of residence. There also is significant cross-time continuity/autostability to some of these environmental influences (e.g., family conflict, parental distress, stress [42, 51] (Glaser et al., 2014; Jester et al., 2005). (Because of space limitations, citations for these and all other pathway relationships are not able to be listed here. A complete listing is available from the senior author.)

FUTURE WORK AND CONCLUDING COMMENTS

In ending, we comment briefly on issues that are significant next-step challenges for the field to address: (1) the need for a more definitive understanding of the role that early use of alcohol plays in damage to brain, and an understanding also of whether or not such damage is reversible; (2) the need to provide a more articulated roadmap of what factors play a role in the development of resilience to disorder, within a risk structure that tends to encourage a

downward progression; (3) the challenge to articulate the translational implications of the burgeoning knowledge base about the brain's development and its functional operations as they translate into new treatments; (4) relatedly, the detailed understanding of mechanistic structure is not only about neural circuitry but also about the multilevel/cross-domain/cross-time evolution of risk into disorder. This understanding should translate into new foci for early identification of risk and new strategies for bringing about change, via pathways that are currently completely out of the purview of both prevention scientists and clinicians. This is the fourth obvious challenge.

Does Early Use of Alcohol Damage the Brain?

For almost a decade, there has been considerable speculation, and some evidence, that early use of alcohol damages adolescent brain in ways that may be irreversible (Zeigler et al., 2005). Given that this era is a time of increasing use and increasing heavy use, ending in consumption levels that are usually highest in the individual's lifetime, the issue is of very large public health importance. These assertions have been largely based on the animal literature (Spear & Varlinskaya, 2005), and studies assessing structural and functional differences in neurodevelopment between heavy and nonheavy using adolescents (Brown & Tapert, 2004). Our review in the previous section describes this work in some detail, and suggests some of the human studies that will need to take place to more definitively answer this question, One of the major impediments to getting a clear answer is that the definitive methodology to address the question is prospective research, so even studies begun today will take some time to provide an answer. Furthermore, although the percentage is small, the heaviest users and those at highest risk for later problem use and disorder are likely to have begun drinking prior to age 12. In addition, the highest risk group is more likely to come from high adversity environments (Buu et al., 2009), hence are exposed to a high level of environmental insults, including stress, accidents, and head injury. Prospective research begun this early is quite uncommon, and even less common are studies that recruit this early and simultaneously are carrying out assessments of neural structure and function and genetic variation. In response to this dilemma, the National Institute on Alcohol Abuse and Alcoholism recently begun a multisite initiative based out of the University of California, San Diego, with the proper assessment methods that will be following youth for the next five years (NIAAA RFAAA-12–006, 2012). At that point, a more definitive answer should become available.

Identifying the Critical Features That Permit a Resilient Adaptation While Exposed to an Otherwise Damaging Risk Structure

The risk literature has increasingly demonstrated the nestedness and stability of risk; that is, high individual risk and high adversity cluster together and predict hazardous use and poor social adaption over time. Given this major individual and social burden, the prevention challenge is to identify those factors that produce risk offset despite exposure to adversity. Researchers in the past decade have increasingly focused on the need to identify promotive and protective factors as the pathway out of risk, rather than focus on the minimization of risk. One core issue is the extent to which the social environment can be engineered to provide sufficient promotive opportunity to overcome a high risk profile (Ostaszewski & Zimmerman, 2007). Another is the extent to which efforts focused at the individual level can ultimately be strong enough to overcome a dense individual risk profile. Alternative theory and recent work have advocated a public health model as the most viable strategy, whereby the focus of intervention is at the community rather than the individual level (Zimmerman, Stewart, Morrel-Samuels, Reischl, & Franzen, 2011). Given the great public health burden of this set of problems, and the nestedness of risk at the individual level, it is essential that the field develop new techniques, and possibly a new model of resilience, to bring about a reduction in risky outcomes.

Translational Implications of Knowledge About the Operation of the Brain's Functional Response Systems

Neuroimaging work to date suggests that there may be more basic, nonbehavioral methods to determine effectiveness of intervention programming by assessing changes in brain functional response systems in areas identified as most hyper (or hypo) responsive among vulnerable youth. Knowledge of these sites of action and their relationships too risky as well as promotive/risk-preventive behavior needs to continue to be developed. Further, sites of central behavioral importance are logical sites to consider as potential targets for pharmacologic intervention. The utilization of neuroimaging methods to identify such sites of action has not yet been attempted for any areas of vulnerability except those related to attention-deficit/hyperactivity disorder. This work needs to be carried out; it has the potential to open up entirely new areas of prevention activity that focus on the mechanistic operations revealed by this research.

New Avenues and Sites for Prevention by Utilization of GxExD Effects

Within the past decade there has been increasing sensitivity to the possibility that genetic effects upon behavior are more variable and more interactive with environment, than had previously been considered the case (Rutter, Moffitt, and Caspi, 2006). This hypothesis has been fine-tuned, and confirmed in specific instances by uncovering differential susceptibility effects (Belsky & Pleuss, 2009), that is, GxE relationships that produce an adaptive outcome under conditions of positive environmental exposure and the presence of one genetic variant, and a maladaptive outcome with the same variant, under conditions of exposure to the obverse environment. They make the point that what have previously been regarded as diathesis genetic effects are, in a number of instances plasticity effects. However, these effects have not come to light because the range of environmental variation under scrutiny has either not been sufficiently broad, or because of the unawareness of the effect, environmental variation was not sufficiently disaggregated to show the effect. Equally importantly but not well enough exploited, genetic effects do not always operate uniformly across the course of development. Heritability of drinking behavior is lower in early adolescence than it is in emerging adulthood (Bergen et al., 2007). GABRA2 is associated with rule breaking at age 13–14, but not with substance abuse problems across adolescence. At the same time, rule breaking at 13–14 prospectively predicts problematic alcohol use at 17–18. However, problematic alcohol use does not predict rule breaking (Trucco et al., 2014).

This work suggests that GxExD relationships have potential to seriously inform intervention activity. At the least, they suggest that there are some seemingly negative environmental experiences that may be equally informative about what the obverse experience should be to turn the behavior around. They also suggest that there are some developmental periods when sensitivity to environmental experience will make youth more vulnerable to intervention, and some developmental periods where it may be wise to not work at change.

The Promise and Challenge of the Next Decade

Substance use disorders consistently rank in the top 5 among those illnesses contributing to the world burden of disease (Whiteford et al., 2013). And among substances of abuse, alcohol continues to be the most widely used, even despite decreases in youthful involvement over the last decade and relatively parallel increases in marijuana use over the interval. So the topic of this chapter remains a highly relevant and timely one.

During this same interval, the mechanistic understanding of this disorder and its contexts of operation has expanded dramatically, to the point that research now operates at all the levels of analysis we have described. Much of the science is quite new, parochial, and to a degree rudimentary, but the fact that some of these domains of effect were not even identifiable 5–10 years ago indicates the level of progress that has taken place. Hopefully over the next decade our ability to move the science from relatively remote and abstract to concrete and translatable will increase dramatically. It needs to, if the science is to deliver on the promises it has made to the general public about this major set of public health problems.

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CHAPTER 19

Substance Use and Substance Use Disorders

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Substance use and substance use disorders are the focus of substantial research efforts in part because of their enormous public health significance. Worldwide, despite substantial regional variation, recent estimates place tobacco and alcohol use as two of the top three factors that determine the global burden of disease, death, and disability, with illegal drug use ranked as number 19 (Lim et al., 2012). Moreover, in addition to the worldwide burden of premature mortality and disability, substance use creates a substantial economic burden. For example, the costs associated with alcohol use in middle-income and high-income countries are more than one percent of their gross domestic products (Rehm et al., 2009). A similar picture can be seen in the United States. In the United States, cigarette smoking remains the single largest preventable cause of death and disability (Centers for Disease Control and Prevention, 2008), and the total costs of the use of alcohol, tobacco, and illegal drugs sum to $559 billion dollars per year (National Institute on Drug Abuse, 2008). In part, the high burden of substance use for mortality, morbidity, and economic cost is due to its high prevalence. For example, recent U.S. data show that 19.5% of individuals are current cigarette smokers (King, Dube, & Tynan, 2012), 2% have current *DSM-IV* drug disorders (10% lifetime; Compton, Thomas, Stinson, & Grant, 2007), and 8.5% have current *DSM-IV* alcohol disorders (30% lifetime, Hasin, Stinson, Ogburn, & Grant, 2007).

Drugs have been used in one form or another since the beginning of recorded history, for multiple purposes (including religious, recreational, and medicinal purposes). However, conceptualizations and views of drug use and drug-related problems show marked historical and social change. In terms of modern history in the United States, the early twentieth century was a time of permissive attitudes and widespread availability of substances including opiates and cocaine. Indeed, some substances were viewed as having medical benefits. Modern antidrug regulation in the United States began with the Harrison Narcotic Act of 1914 and alcohol Prohibition in 1920, and strict laws were still in place in the 1950s (Musto, 1995). After the wave of drug use following the 1960s, the modern war on drugs began under the presidency of Richard Nixon. This also marked the beginning of modern tobacco regulation in the United States. For example, health warnings on cigarette packs in the United States were introduced in 1969. Historically, at various times, drug addiction has been viewed as a medical problem, socially learned behavior, a moral weakness, criminality, and (most recently) a chronic brain disorder (Leshner, 1997).

Adolescence is the typical age of substance use onset, and some experimentation with substance use during adolescence is relatively common. This can be seen in U.S. epidemiological data including national school-based surveys such as Monitoring the Future (MTF; Johnston, O'Malley, Bachman, & Schulenberg, 2013) and the Youth Risk Behavior Survey (YRBSS; Centers for Disease Control and Prevention, 2012) as well as household surveys such as the National Survey on Drug Use and Health (NSUDH, SAMHSA, 2012) and combined school and household samples in the National Comorbidity Survey Adolescent Supplement (Swendsen et al., 2012). For example, in the National Comorbidity Survey (2001–2004 data), 78.2 % of adolescents (aged 13–18 years) had used alcohol and 24.4% had used an illegal drug. In 2011, 22% of high school students in the YRBSS and 24% of twelfth graders in MTF reported drinking five drinks on a single occasion within the past month and 18–19% of participants in the two surveys were current (past month) cigarette smokers. Marijuana is the most commonly used illegal drug, with current use reported by 23% of high school students in the YRBSS and 7.9% of those aged 12–17 years in the NSUDH. Daily marijuana use was reported by 6.6% of twelfth graders in 2011 in MTF.

Importantly, although some substance use is relatively common during adolescence, this does not imply that adolescent substance use is benign. Substance use is associated with the leading causes of adolescent mortality (accident, homicides, and suicides; Centers for Disease Control and Prevention, 2010a). Among high school students in the YRBSS, 24% reported having ridden with a driver who had been drinking and 8.2% reported driving after drinking, illustrating the potential for alcohol-related traffic accidents for many adolescents. Some of the associated risk for morbidity and mortality stemming from adolescent substance use can be attributed to the fact that adolescent consumption patterns are particularly risky. For example, compared with adults, adolescents drink alcohol on fewer days (i.e., lower frequency of use), but when they drink it is at levels of higher quantity, producing a binge pattern that creates high risk for alcohol-related consequences (Masten, Faden, Zucker, & Spear, 2008). Moreover, the fact that adolescent substance use occurs in peer contexts that are outside of adult supervision also exposes them to excess risk for negative consequences.

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CHAPTER OVERVIEW

The current chapter applies a developmental psychopathology perspective to the literature on substance use disorders. As suggested by a developmental psychopathology perspective (see, e.g., Cicchetti & Toth, 2009), we consider substance use disorders in relation to developmentally normative substance use patterns and we consider etiological models that are multidisciplinary (i.e., biopsychosocial) and multilevel (e.g., we consider gene–environment interplay). Moreover, as suggested by the developmental psychopathology perspective, we consider multiple etiological pathways to substance use disorder (equifinality) but note that pathways are probabilistic, such that not all individuals exposed to identical risk factors will develop disorder (multifinality; see, e.g., Cicchetti & Toth, 2009).

We first define clinical substance use disorders according to recent American Psychiatric Association taxonomies (i.e., *DSM-IV* and *DSM-5*; American Psychiatric Association, 2000; 2013). We then describe epidemiological data including demographic correlates and substance use patterns, including a consideration of gateway theory, which hypothesizes that earlier substance use has a causal effect on later use. We then review evidence for age-related trajectories of substance use outcomes and the extent to which ages of onset and offset inform etiological theory, including the significance of age of substance use onset and time to disorder. Next we examine three major biopsychological etiological pathways, integrating risk factors from multiple levels and considering gene–environment interplay. We consider the deviance proneness or externalizing pathway, which conceptualizes substance use disorders within the externalizing spectrum; the stress and negative affect pathway; and the substance use effects pathway, which focuses on the pharmacological effects of substance use as motivators for consumption. For each of these pathways, we consider implications for prevention and treatment of substance disorders. Because none of these three pathways focus on macro-environments, we next consider the roles of larger social influences including neighborhoods, schools, media, and public policy. Finally, we conclude the chapter with suggestions for future research.

CLINICAL SUBSTANCE USE DISORDERS

In addition to risk for physical morbidity and mortality, adolescents are at risk of developing clinical substance use disorders. The *Diagnostic and Statistical Manual,* 4th ed., text revision (*DSM-IV-TR*; American Psychiatric Association, 2000) defined two major SUDs: substance dependence and substance abuse. Substance dependence is defined as:

> A maladaptive pattern of use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following symptoms occurring at any time in the same 12-month period: (1) tolerance, (2) withdrawal, (3) the substance is often taken in larger amounts or over a longer period than intended, (4) a persistent desire or unsuccessful efforts to cut down or control substance use (5) a great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects, (6) important social, occupational, or recreational activities are given up or reduced because of substance use, and (7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. (P. 197)

The *DSM-IV* defined substance abuse as:

> A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following occurring within a 12-month period: (1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home, (2) recurrent substance use in situations in which it is physically hazardous, (3) recurrent substance-related legal problems, and (4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance. (P. 198)

Because dependence is thought to be more severe, individuals who meet criteria for dependence were not diagnosed with abuse.

However, the validity of the distinction between substance abuse and dependence has been called into question. For example, item-response theory (IRT) studies show that some dependence criteria (e.g., tolerance, impaired control) are less severe than are some abuse criteria (e.g., legal difficulties; Kahler & Strong, 2006; Saha, Stinson, & Grant, 2007). Moreover, factor analyses have not confirmed two-factor solutions consistent with abuse and dependence (e.g., Harford & Muthen, 2001; Proudfoot, Baillie, & Teeson, 2006). For these reasons, the most recent taxonomy (*DSM-5*) drops the distinction between abuse and dependence. Instead there is a single substance use disorder diagnosis, which is based on 11 symptoms. Legal problems were dropped as a symptom but craving was added. There are concerns that the *DSM-5* criteria will be too liberal and overdiagnose substance disorder, producing high prevalence rates and cases with low severity (Martin, Steinley, Verges, & Sher, 2011). However, *DSM-5*

was designed to yield prevalence rates roughly comparable to *DSM-IV,* and, thus,it may produce little change in the population prevalence of substance use disorder.

Adolescent substance use disorders are diagnosed using adult criteria, although the developmental appropriateness of this practice has been questioned (e.g., Chen & Anthony, 2003; Chung & Martin 2005). Based on recent epidemiological data, a significant minority of adolescents develop a clinical substance use disorder. Rates in the most recent NSUDH data were 6.9% (ages 12–17) and 18.6% (ages 18–25) for alcohol disorder and 3.8% (ages 12–17) and 14.4% (ages 18–25) for drug disorder, with a rate of 11.4% lifetime disorders among ages 13–18 in the National Comorbidity Survey-Adolescent Supplement (Merikangas et al., 2010).

EPIDEMIOLOGICAL TRENDS IN ADOLESCENT SUBSTANCE USE

Although some substance use experimentation is common in adolescence, the prevalence of use of specific substances shows substantial variation over time with new drugs becoming popular and then waning in prevalence, in parallel with changes in perceived risk of use. A recent example can be seen in the use of bath salts, a designer drug that came to media attention in 2010 but for which use was declining by 2012 (Johnston et al., 2013). In addition to the introduction of new drugs that show brief periods of popularity, older drugs sometimes show resurgent popularity, after knowledge about the dangers of use have been lost from the culture. Johnston et al. (2013) referred to this phenomenon as generational forgetting. At the time of this writing (2013), there have been continuing and substantial declines in both adolescent alcohol use and cigarette smoking, and these declines track significant public health efforts and social policies targeted at these behaviors. The Monitoring Future Data also show 2012 declines in the use of ecstasy, Vicodin, and OxyContin. In contrast, however, adolescent marijuana use has increased, (albeit stabilized in 2012; Johnston et al., 2013), along with increases in its perceived acceptability and availability and lowered perceived risk. This may reflect broader societal trends toward increased acceptance of marijuana use, as seen in state policies concerning decriminalization and medical marijuana. Similarly, although the prevalence of cigarette smoking has decreased substantially, a variety of new tobacco products have recently been introduced, including dissolvable forms of smokeless tobacco and e-cigarettes. These new products have the potential to achieve harm reduction benefits if individuals switch from combustible cigarettes to these noncombustible alternatives. However, they also have the potential to perpetuate cigarette smoking or even to increase risk for smoking if the reinforcing effects of nicotine result in these products serving as a gateway to smoking (Hatsukami, Ebbert, Feuer, Stepanov, & Hecht, 2007). An important direction for future epidemiological research is to examine the effects of these alternate tobacco products on smoking prevalence.

Another focus of concern in recent years has been adolescent misuse of prescription medication. One review of the literature (Young, Glover, & Havens, 2012) found that, among 12–17-year-olds, misuse of pain medication and stimulants were most common, with past year rates of 4–11% for pain medication and 1.7–3% for stimulants. These trends are somewhat difficult to assess in the Monitoring the Future data because mention of some specific prescription drugs were only recently introduced. However, the general trend in categories of use suggests that misuse of prescription pain medication and tranquilizers began to rise in the early 1990s and has only recently stabilized or slightly declined (varying with different substances). The misuse of Adderall may be an exception to this decline, because the Monitoring the Future data showed a small (nonsignificant) increase for twelfth graders. Moreover, the misuse of Adderall may be even greater for college students than for high school students (and higher for college students than for their age peers who do not attend college (Kaye & Darke, 2012). Wilens et al. (2008) reviewed the literature and found past year rates of 5–9% through Grade 12 but 5–35% in college students. Not surprisingly, the most common reported reason for misuse of Adderall is to achieve cognitive and performance enhancement (Kaye & Darke, 2012).

These trends over time in adolescent substance use prevalence have several implications for understanding the etiology of substance use and for public health interventions. Johnston et al. (2013) argued that the use of specific drugs shows volatility over time, such that prevalence rates change in response to societal changes in acceptability and perceived risk, whereas the proportion of adolescents who engage in some form of substance stays more stable. The changes in use of specific substances argue for the importance of continued public health messages about consequences and risk, combined with restrictions on availability and access. However, the greater stability of the proportion of adolescents who engage in some form of substance use raises the possibility of drug substitution.

Moreover, changes in prevalence over time illustrate the importance of cultural/historical context in shaping

substance use behavior. Indeed, these cultural-historical influences can produce long-lasting cohort effects in substance use, such that specific birth cohorts carry their substance use involvement over the life span from adolescence to old age. This can be seen in an analysis of the Monitoring the Future Data in which adolescents from birth cohorts showing anti-drinking social norms had less drinking than did those whose birth cohorts were more approving or tolerant of alcohol use (Keyes et al., 2012). Indeed, the Baby Boomer cohorts have been marked by high levels of substance use involvement across different age periods, and the current aging of the Baby Boomers has led researchers to predict that there will be higher levels of substance use among older individuals in the coming years (Colliver, Compton, Gfroerer, & Condon, 2006). Moreover, these cohort effects have implications for etiological theory in terms of influences that propel drug use in different historical periods. For example, an analysis of twin data from the National Survey of Midlife Development suggests that the heritability of smoking differs among birth cohorts from 1920 to the 1960s (Boardman, Blalock, & Pampel, 2010).

RELATIONS WITH DEMOGRAPHIC FACTORS

Perhaps the strongest demographic predictor of substance is age, with adolescence being the typical time of substance use onset and escalation to higher levels of use. Emerging adulthood (age 18 to the early to mid-20s) is the age period of peak rates of substance use as well as clinical substance use disorders. Because of the importance of age-related trajectories of substance use and substance use disorders, this literature is reviewed in a separate section below. Here we discuss relations between substance use and socioeconomic status, race/ethnicity, and gender.

The relation between socioeconomic status (SES) and substance use is complex, characterized by conflicting data, many null findings, and possible variation with age, race/ethnicity, and the specific substance under consideration. Reviews of longitudinal studies have found no effects of childhood SES on later alcohol disorders (Wiles et al., 2007) but significant effects of low childhood SES on elevations in adult marijuana use (Daniel et al., 2009) and adolescent marijuana use (Lemstra et al., 2008). Lower SES also predicts greater cigarette smoking particularly in high SES neighborhoods (Mathur, Erickson, Stigler, Forster, & Finnegan, 2013).

Because many studies do not control for the effects of race/ethnicity, effects of SES could be due to race/ethnicity. Data from the Monitoring the Future Study (Bachman, O'Malley, Johnston, Schulenberg, & Wallace, 2011) found that, among non-Hispanic Caucasian adolescents, those with better educated parents reported less use of alcohol and cigarettes in eighth and tenth grades, but those effects dissipated by Grade 12. No parent education effects were detected for African American and Hispanic adolescents. Bachman et al. (2011) suggest that there are catch-up effects among non-Hispanic Caucasian adolescents from well-educated families. Similar results were found in the Add Health study (Humensky, 2010) in that higher parent SES predicted more early adult marijuana and binge drinking and the same result was found in the Panel Study of Income Dynamics data (Patrick, Wightman, Schoeni, & Schulenberg, 2012).

Similar complexity is found in studies of neighborhood SES. Karriker-Jaffe's (2011) review found more significant effects of neighborhood disadvantage for adults than for adolescents and reported that risk for substance use was associated with neighborhood advantage for adolescents. Thus, it is possible that low SES is a risk in childhood with a more complicated pattern in adolescence. The association with low SES in adulthood likely reflects both the causes and the results of substance use. Other moderators besides age may also contribute to the complex pattern of findings. For example, Trim and Chassin (2008) found that neighborhood disadvantage was associated with increased alcohol use among children of alcoholic parents whereas the opposite was true for children of nonalcoholic parents.

Finally, it is possible that the complex pattern of results reflect curvilinear relations, such that adolescent substance use is elevated at the extremes of poverty (Hawkins, Catalano, & Miller, 1992) and affluence (Luthar & Barkin, 2012), although the confounding effects of race/ethnicity preclude strong conclusions. For affluent adolescents, Luthar and Barkin (2012) suggest that risk factors for substance use include a lack of parental sanctions for substance use behavior. In terms of poverty, Costello, Erkanli, Copeland, & Angold (2010) found that American Indian children who received income supplements as a result of a casino opening showed lower rates of adult alcohol and cannabis dependence than did their non-Indian peers who did not receive these income supplements (suggesting a causal effect of poverty) and that material hardship in adolescence predicted a greater likelihood of diagnosed substance use disorder.

In terms of ethnicity, rates of adolescent substance use are highest for American Indians, followed by non-Hispanic Caucasians and Hispanics, with lower rates reported for African American and Asian adolescents

(Johnston et al., 2013; Swendsen et al., 2012). In addition, rates vary for different Hispanic subgroups (Caetano, Ramisetty-Mikler, & Rodriguez, 2009) and by nativity and time in the United States, with immigrants generally showing lower rates than native U.S.–born individuals. However, there are also complex interactions with age. For example, in the Monitoring the Future Data, Hispanic adolescents have higher rates than other groups at eighth grade, but this disappears by twelfth grade, perhaps reflecting greater school dropout among Hispanic adolescents than other groups (Johnston et al., 2013). Similarly, although in adolescence, African Americans smoke cigarettes at substantially lower rates than do non-Hispanic Caucasians, this difference reverses in adulthood, in part because of racial differences in educational attainment and marital status (Kandel, Schaffran, Hu, & Thomas, 2011). There are also complex relations between race and multiple dimensions of substance use involvement. For example, African Americans are less likely to use alcohol and generally drink at lower levels than do non-Hispanic Caucasians in both adolescence and adulthood. Yet they are more likely to experience alcohol-related problems even at equivalent levels of alcohol intake (Zapolski, Pederson, McCarthy, & Smith, 2013). Although the reasons for this are unclear, Zapolski et al. (2013) proposed multiple factors may contribute to a higher level of alcohol-related problems for African Americans compared with other groups, including drinking being more likely to occur in higher risk locations (e.g., low SES neighborhoods) that also carry increased risk for legal sanctions, self-reports that underestimate the amount of alcohol that is consumed, heritable differences in sensitivity to alcohol effects, and attitudinal intolerance of alcohol use in the African American community that leads to negative social reactions to drinking.

In terms of gender differences in prevalence, the Monitoring the Future data (Johnston et al., 2013) show that, during adolescence, males have slightly higher levels of substance use although this varies with the type of substance in question. For example, males show higher rates of heavy drinking and smokeless tobacco use than do girls, but there are few gender differences in overall alcohol consumption or cigarette smoking. Gender differences tend to increase at older ages (Johnston et al., 2013; Swendsen et al., 2012). Moreover, there is some evidence that gender differences have been narrowing for more recent birth cohorts (Keyes et al., 2012), suggesting that changing social norms may influence the extent of gender differences in substance use behaviors.

Substance use is also related to family structure, with offspring in divorced families showing higher rates. However, because divorce is associated with many other environmental risk factors (e.g., family conflict) and with genetic risk for substance use outcomes (e.g., parental alcohol and drug disorders), studies have attempted to identify the causal significance of divorce. Genetically informed studies including adoption and children of twins designs suggest that divorce has an environmentally mediated effect (D'Onofrio, Turkheimer et al., 2007; O'Connor, Caspi, DeFries, & Plomin, 2000). For example, adopted children whose parents divorce have higher rates of substance use than do adopted children from intact families (O'Connor et al., 2000). Moreover, parental divorce is associated with lifetime diagnoses of alcohol dependence over and above parental alcohol problems (Thompson, Lizardi et al., 2008). Given these findings, it is important to consider potential mechanisms by which parental divorce might increase risk for offspring substance use. Indeed, there is evidence to suggest that divorce-related impairments in parenting and parent–child relationship quality may be important mediating mechanisms. Preventive interventions that focus on improving parenting have shown beneficial effects on adolescent substance use for children from divorced families (Sandler, Schoenfelder, Wolchik, & MacKinnon, 2011) and changes in parental monitoring, discipline, and parent–child relationship quality have been shown to be significant mediators of these intervention effects (Sandler et al., 2011).

USE OF MULTIPLE SUBSTANCES: PATTERNS OVER TIME

Adolescents tend to use multiple substances so that the use of any one drug is a risk factor for the use of other drugs (Palmer et al., 2009). Indeed, it has been argued that adolescent substance use follows a series of predictable stages such that the use of licit substances (alcohol and tobacco) is followed by marijuana use and then other illegal drugs. This stage-sequence model has been referred to as the gateway theory (Kandel, 1975) because licit substances are presumed to serve as a gateway to the use of illegal drugs. Although there are both retrospective and longitudinal data consistent with this sequence, this theory remains controversial. First, the sequence of use of different substances is not invariant across subgroups. For example, some studies of African American samples have shown that cannabis use precedes the use of cigarettes (Vaughn, Wallace, Perron, Copeland, & Howard, 2008) and alcohol (Sartor et al., 2013). Second, and most important, it is unclear whether or not the use of earlier substances in the

sequence plays a causal role in the use of drugs later in the sequence as implied by the gateway theory or, instead, whether adolescents' use of multiple substances is caused by common correlated risk factors, including a common genetic liability as has been reported for adolescent alcohol, tobacco, and marijuana use (Hopfer, Crowley, & Hewitt, 2003; Kendler, Schmitt, Aggen, & Prescott, 2008). For example, considering whether marijuana use serves as a gateway to other illegal drug use, some studies have found that the effect of earlier marijuana use on later illegal drug use is eliminated when correlated risk factors are considered (e.g., Van Gundy & Rebellon, 2010) although others find that the effect of earlier marijuana is maintained (albeit weakened) after consideration of potential confounders (Fergusson, Boden, & Horwood, 2006).

In evaluating whether earlier use of one substance might play a causal role in the later use of other substances, it is important to identify possible theory-based mechanisms by which such a causal effect could occur. Cross-sensitization (i.e., the process by which the use of one drug increases responses to other drugs) may be one mechanism underlying the gateway model. Sensitization effects have been shown in animal data. For example, pretreatment with cannabis increases opiate use (Ellgren, Spano, & Hurd, 2007). Pretreatment with nicotine increases cocaine reward (McQuown, Beluzzi, & Leslie, 2007) and also increases conditioned place preference and locomotor activation in response to cocaine (mediated through changes in gene expression). However, this result was obtained only when cocaine and nicotine were later administered together (Levine et al., 2011). The level of quantity, frequency, and duration of use that would be needed for such mechanisms to operate among human adolescents are not clear. In addition to common risk factors (including genetic risk) and sensitization as potential explanations, the early use of licit drugs or marijuana may increase later drug use indirectly because adolescent users of licit drugs or marijuana may join peer groups that promote the use of other drugs or who provide greater access to other drugs (see Lynskey & Agrawal, 2009).

Finally, in considering patterns of use of multiple drugs, it is important to consider the possibility that the use of one drug can substitute for another. The possibility of substitution effects is important from a policy perspective. For example, researchers have tested whether the minimum legal drinking age of 21 may inadvertently increase marijuana use before age 21. Using longitudinal data, Crost and Guerrero (2012) found decreases in marijuana use at age 21, the age at which alcohol use becomes legal and the age at which alcohol use increased sharply. They argue that alcohol and marijuana use can be substitutes and that policies for increasing the minimum legal drinking age can have negative unintended consequences of increasing other drug use. Although the question of drug substitution is particularly important, given the potential for unintended negative consequences of policy interventions such as increasing taxes or restricting access to substances, several cross sectional studies comparing states with differing drinking ages have not found alcohol and marijuana substitution effects (see Crost & Guerrero, 2012 for a review).

AGE-RELATED TRAJECTORIES OF SUBSTANCE USE: TYPICAL AGE-RELATED PATTERNS

As noted earlier, the typical age of onset of substance use is during adolescence and there are multiple developmental influences that likely explain this finding. Adolescence is characterized by increased autonomy from parents and greater time spent in peer contexts and outside of parental supervision. Theoretical models such as problem behavior theory (Jessor & Jessor, 1977) argue that adolescents are motivated to display independence and an image of adult status. Some forms of substance use such as alcohol and cigarette smoking are age-graded behaviors that are legal for adults but not for adolescents. Thus, use of these substances can display a social image of precocity and independence, making adolescence a period of particular risk for substance use behavior.

In addition to these psychosocial mechanisms, recent models of adolescent development have suggested that this period is characterized by a disjunction between trajectories of reward seeking and cognitive control driven by neurobiological processes of adolescent brain development. Specifically, reorganization of the approach system and slow maturation of the control/regulation system are thought to create an asynchrony such that increases in motivation for positive arousal go unchecked by an immature capacity for effortful regulation (Somerville, Jones, & Casey, 2010; Steinberg, 2008). The notion that there are neurobiological underpinnings that predispose adolescents to risk-taking behavior is consistent with an evolutionary perspective, which points to increases in risk taking and exploration during adolescence across multiple animal species and suggests that there is adaptive value of adolescent exploration and risk-taking for promoting independence and mate selection (Ellis et al., 2012).

In terms of the approach system, changes in dopaminergic systems, including density of receptors in cortical and

subcortical regions (e.g., ventral striatum), are thought to underlie increases in the salience of reward and sensation seeking (Chambers, Taylor, & Potenza, 2003). Several lines of evidence support this idea. Compared with adults, adolescents are more behaviorally and emotionally reactive to monetary incentives (Hardin, Schroth, Pine, & Ernst, 2007). Adolescents are more sensitive to positive feedback during affective decision making compared with adults and children (Cauffman et al., 2010). Reward sensitivity and sensation seeking, an individual difference thought to be linked to strong sensitivity to reward (Dawe, Gullo, & Loxton, 2004; Knyazev, Slobodskaya, Kharchenko, & Wilson, 2004), increases during adolescence (Colder, Hawk, et al., 2012; Crawford, Pentz, Chou, Li, & Dwyer, 2003). Converging lines of evidence from imaging studies suggest that adolescents compared with adults are more sensitive to reward and process reward and risk information in a way that increases the likelihood of sensation seeking and risky behavior (Bjork, Smith, Danube, & Hommer, 2007; Casey, Jones, & Hare, 2008; Van Leijenhorst et al., 2010).

With respect to the control/regulation system, pruning and differentiation of synapses and increased myelination in the prefrontal cortex continue well into adolescence, and these changes presumably enhance efficiency of the system and connectivity between cortical structures (Geidd et al., 1999; Somerville et al., 2010). Behavioral studies show continued improvement on cognitive tasks that require recruitment of the control/regulation system (Crone & van der Molen, 2004; Conklin, Luciana, Hooper, & Yarger, 2007; Hooper, Luciana, Conklin, & Yarger, 2004). Imaging studies show that adolescents are less efficient at recruiting the control/regulation system on tasks requiring cognitive control (Durston et al., 2006) and that improved performance on these tasks from childhood to adulthood is associated with increased activation of prefrontal cortical areas and connectivity between cortical and subcortical structures (Somerville et al., 2010).

Although considerable evidence has accumulated for the role of adolescent brain development in risk taking behavior and substance use, there are presumably individual differences in timing of these processes. One prediction is that youth who show more rapid changes in the approach system and commensurate increases in motivation for positive arousal, or particularly slow maturation of the prefrontal cortex and immature regulatory capacity, or both are expected to be at increased risk adolescent substance use. Few longitudinal studies have examined such questions. Two studies found that more rapid increases in behavior indicative of motivation for positive arousal (e.g., sensitivity to reward and sensation seeking) during adolescence were associated increases in drug use (Colder, Hawk et al., 2012; Crawford et al., 2003). Quinn and Harden (2013) found that slower declines in motivation for positive arousal in late adolescence were associated with escalation of drug use. Another possibility is that drug use itself can disrupt adolescent brain development, resulting in transactions between drug use and changes in the approach and control/regulation systems and a feed forward process that results in escalation to disorder (Squeglia, Jacobus, & Tapert, 2009).

If adolescence is the typical age of substance use onset with peaks in emerging adulthood, the early to mid-20s mark the typical ages of substance use decline, a phenomenon often referred to as maturing out. Psychosocial explanations of this phenomenon have suggested that it is driven by the increased responsibilities associated with the acquisition of adult roles such as marriage, parenthood, and employment that occurs during these ages. Yamaguchi and Kandel (1985) termed this process role socialization. That is, when behaviors are incompatible with the norms and obligations of social roles, an individual needs to resolve this incompatibility either by desisting from the behavior or by leaving the role. Indeed, the relation between role acquisition and declines in substance use has been empirically supported (Bachman et al., 2002), particularly for family roles (Staff et al., 2010). Of course role transitions can occur at many ages so their effects will not be restricted to early adulthood. Moreover, age-atypical role transitions such as an early transition to parenthood have not shown protective effects on substance use behavior (Little, Handley, Leuthe, & Chassin, 2009).

Although research has confirmed the relation of role transitions to changes in substance use behavior, there are other changes that occur in the early to mid-20s that could also explain age-related declines in substance use. As described earlier, over the course of adolescence and into the mid-20s, there is a gradual maturation of cognitive control systems (Paus, 2005; Steinberg, 2008), and these increases in cognitive control would be expected to reduce risk-taking behavior in general, and substance use more specifically.

Moreover, accompanying changes in cognitive control and the acquisition of adult roles and responsibilities are changes in personality. Personality is not a fixed characteristic that is immutable over the life course but, rather, shows fairly dramatic normative changes throughout adolescence and later adulthood (e.g., Roberts, Walton, & Viechtbauer, 2006). Increases in psychosocial maturity in early adulthood are demonstrated in decreased negative affectivity and increased conscientiousness and related

self-control. Indeed, recent studies have demonstrated that individual differences in age-related changes in personality including declines in behavioral disinhibition/impulsivity and negative emotionality/neuroticism and increases in conscientiousness are correlated with declines in alcohol use in emerging adulthood and early adulthood (Littlefield, Sher, & Wood, 2009). Importantly, the association between personality change and change in drinking in emerging adulthood persists even when adult role occupancies are considered (Littlefield et al., 2009). Moreover, even in late adolescence when (on average) rates of alcohol use and levels of use are increasing at the same time that impulsivity and sensation seeking) are decreasing, smaller decreases in these traits are associated with bigger increases in substance use (Quinn & Harden, 2013).

Of course, the association between age-related changes in personality and changes in substance use may reflect either the influence of personality on substance use or the influence of substance use on personality. The notion that substance use influences personality is consistent with neurobiological findings showing that neuroadaptation to chronic substance use creates a persistent negative affective state motivating continued use (e.g., Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Koob & Le Moal, 2008). What is less clear is the degree to which less severe substance use patterns alter personality traits and, if they do, how persistent such changes are. There is some recent evidence that alcohol use might influence age-related personality change, but the results are not totally consistent. Hicks, Durbin, Blonigen, Iacono and McGue (2012) found that individuals whose alcohol disorder began in adolescence and was persistent into young adulthood, did not show normative declines in negative emotionality, and suggested that alcohol use interfered with age-related declines in negative emotionality. However, Littlefield, Vergés, Wood, and Sher (2012) found that the effects of alcohol involvement on personality appeared to operate on shorter timeframes and to be dependent upon the developmental period under investigation (see also Quinn, Stappenbeck, & Fromme, 2011). At this point, the relation between personality change and substance use patterns has yet to be fully characterized but existing data suggests that there is a fairly strong association and that the relation between personality and substance use is a dynamic one.

Finally, although the prevalence of substance use and substance use disorders is lower after the mid-20s, we now know that maturing out is more complex than previously thought. For example, Vergés et al. (2013), using NESARC data, found that rates of persistence of drug disorders did not change with age and that role transitions influence drug disorders at many ages not just during emerging adulthood.

INDIVIDUAL VARIABILITY IN SUBSTANCE USE TRAJECTORIES: THE SIGNIFICANCE OF AGE OF ONSET AND TIME TO DISORDER

Both longitudinal and cross sectional research suggests that earlier age of onset of tobacco, alcohol, and illegal drug use is associated with higher risk for the development of a substance use disorder (Grant & Dawson, 1998). However, there is considerable controversy about whether this association represents a causal relation (e.g., McGue & Iacono, 2008; Odgers et al., 2008). Some studies suggest that controlling for correlated risk factors eliminates the effect of age of alcohol onset on later alcohol disorder but not the effect of early drug use onset on later drug disorder (King & Chassin, 2007). However, analyses using propensity score approaches provide support for the effect of early age of onset on later problems (Odgers et al., 2008).

Because age of first exposure in humans is heritable (at least for alcohol), it has been argued that the association between early onset of substance use and later substance use disorder may be due to a shared genetic risk for disinhibition (McGue, Iacono, Legrand, & Elkins, 2001). Genetically informative studies provide conflicting findings. Early onset of smoking is associated with increased likelihood of developing tobacco dependence (e.g., Breslau, Fenn, & Peterson, 1993) and one recent twin study found that among twins discordant for age of initiating smoking, the twin who started earlier was more likely to develop dependence (Kendler, Myers, Damaj, & Chen, 2013). There may a causal role for early cannabis exposure as well although twin studies (e.g., Agrawal, Neale, Prescott, & Kendler, 2004; Lynskey et al., 2003) suggest that much of the association is due to common genetic and environmental vulnerabilities.

Theoretically, it has been proposed that a causal relation between early onset of use and later substance use disorder could be due to differential sensitivity to substance use effects for adolescent compared with adult exposure. Accumulating evidence suggests that adolescents may be particularly sensitive to the neurotoxic effects of various substances and that adolescent exposure may produce durable neurocognitive changes. This is most likely due to the fact that adolescence is a period marked by extensive changes in the maturation of the brain characterized by extensive synaptic pruning and development of the frontal lobes (Clark, Thatcher, & Tapert, 2008; Crews, He, &

Hodge, 2007; Selemon, 2013) creating vulnerabilities to exogenous substances that affect the brain (as well as endogenous, stress-induced processes). For example, heavy exposure to alcohol in adolescence has been associated with structural and functional brain deficits, and also deficits in cognitive functioning (e.g., Hanson, Medina, Padula, Tapert, & Brown, 2011). The associated neurocognitive deficits, especially those associated with deficits in prefrontal and limbic systems (Monti et al., 2005), could pose added risk for heavier substance use and engagement in a range of externalizing behaviors (e.g., Bava & Tapert, 2010). Although a definite causal relation in humans has yet to be established due to the paucity of truly prospective designs that first assess youth prior to their first substance use exposures, rodent models of adolescent ethanol exposure (Crews, Braun, Hoplight, Switzer, & Knapp, 2000; Spear, 2000) demonstrate that adolescence appears to be a time of heightened sensitivity to persistent neurologic damage (i.e., greater deficits associated with adolescent exposures than with preadolescent or adult exposures). Adolescent cannabis exposure is associated with risk for the development of psychotic illness (Moore et al., 2007; Semple, McIntosh, & Lawrie, 2005) and the timing of the exposure appears to be limited to adolescence (and possibly to individuals with specific genotypes; Caspi et al., 2005).

In addition to age-specific vulnerabilities for neurotoxic effects that may increase risk for later substance use, adolescents may be differentially sensitive to the reinforcing effects of substance use. For example, compared with adults, adolescents experience less sensitivity to the impairing effects of alcohol, more acute tolerance, but more sensitivity to rewarding effects and social facilitation (Spear, 2011). This pattern should raise risk for adolescent heavy alcohol use and thus raise risk for subsequent alcohol disorder. Moreover, although there are few studies (Spear, 2011), some animal data suggest that adolescent exposure produces heavier adult self-administration (Rodd-Henricks et al., 2002) or greater reinforcement than does adult exposure (Adriani, Deroche-Gamonet, Le Moal, Laviola, & Piazza, 2006).

In addition to age of onset, another potentially important aspect of a substance use trajectory is the time that it takes to transition from initial use of a substance to the development of a substance use disorder. Shorter time to disorder (i.e., a telescoped trajectory) gives clues to the processes of vulnerability and protection. Some data suggest that non-Hispanic Caucasians show greater telescoping for alcohol dependence than do African Americans or Hispanics (Alvanzo et al., 2011). Findings of gender differences are mixed. For example, alcohol studies have reported greater telescoping for women (Randall et al., 1999), for men (Keyes, Martins, Blanco, & Hasin, 2010) and no gender differences (Alvanzo et al., 2011). It has also been reported that there is a faster time to alcohol dependence for individuals with anxiety disorder (Kushner, Maurer, Menary, & Thuras, 2011). A limitation of this literature is that, despite the fact that telescoping is a process that occurs over time, much of the data are based on retrospections from cross sectional studies. One study that was able to capitalize more on longitudinal data found greater telescoping effects for both alcohol and drug disorders for children of alcoholic parents and for individuals with externalizing symptomatology (Hussong, Bauer, & Chassin, 2008). Potential mechanisms underlying these findings include the possibility that children of alcoholic parents experience more positive reinforcement (or less aversive effects) from exposure to alcohol and drugs than do children of nonalcoholic parents.

ETIOLOGICAL PATHWAYS: GENERAL AND SUBSTANCE-SPECIFIC BIOPSYCHOSOCIAL MECHANISMS OF RISK AND AGE AND STAGE DIFFERENCES IN RISK PATHWAYS

There are multiple etiological pathways that underlie the development of substance use and substance use disorders, reflecting the developmental psychopathology principle of equifinality. Before reviewing these pathways, it is important to note several critical features of them. First, each of these pathways is characterized by complex gene–environment interplay. As reported in a recent review (Kendler, Chen, et al., 2012) there are substantial heritable influences on substance use disorders, with twin studies suggesting that genetic influences generally account for 40–55% of the variance across different forms of substance use disorders (more for cocaine abuse). However, the magnitude of genetic influence varies not only across different forms of substance use disorder, but also with different stages of disorder (i.e., initiation, heavy use, problem use, and clinically diagnosable disorder) and the magnitude of genetic influence varies with age. The general pattern is that shared environment influences are substantial and strongest at younger ages and at earlier stages of substance use (Kendler, Chen, et al., 2012; Stallings, Gizer, & Young-Wolff, in press). For example, Kendler et al. (2008) analyzed retrospective life calendar data from a large sample of male twins to examine genetic and family environment influences on caffeine, nicotine, alcohol, and marijuana use. They found that

family environment influences declined with age whereas genetic influences increased. Interestingly, however, family environment influences persisted (albeit at lower levels) well into adulthood. Thus, environmental influences can have enduring effects even after the age of leaving home. Perhaps early environment sets the stage for cascading influences that perpetuate substance use over ages (Haller, Handley, Chassin, & Bountress, 2010). Moreover, it is also important to ask why the magnitude of genetic influences on substance use would increase with age. This may reflect greater genetic influences on persistent use that are masked at early ages by developmentally limited experimentation. In addition (as noted by Kendler et al., 2008), the increasing role of genetic influences may reflect greater "niche picking" at older ages. That is, at older ages, individuals have greater ability to choose their own environments. However, although the evidence base from population-based, twin studies on alcohol and tobacco use and disorders is very extensive and reasonably consistent about age differences in heritability, this is far less true for illicit drug use and drug use disorders with the exception of cannabis use and cannabis use disorder (Stallings et al., in press) and so some degree of caution should be expressed in generalizing too strongly across all drugs of abuse.

In addition to age differences, the magnitude of genetic and environmental influences varies across stages of substance use such that environmental influences are stronger for substance use initiation and heritable influences are stronger for substance use problems (Kendler, Chen, et al., 2012). For example, Rhee et al. (2003) found this pattern for alcohol, tobacco, and any drug (but not for marijuana) in a sample including twins, siblings, and adoptees. Twin studies using CCC models have produced similar findings (see Kendler, Chen, et al., 2012). The differing heritabilities for substance use initiation compared with substance-use related problems or disorders raises the importance of examining stage-specific etiological influences more generally. For example, in a study of the development of alcohol dependence, Sartor, Lynskey, Heath, Jacob, and True (2007) found that although externalizing problems was a risk factor for both the initiation of alcohol use and for the development of dependence among users, initiation and dependence (conditional upon those who had already initiated) were associated with distinct predictors. Moreover, multivariate twin studies of alcohol dependence suggest that different symptoms of dependence may have different etiologies (Kendler, Aggen, Prescott, Crabbe, & Neale, 2012). These types of findings highlight that we need to think about the continuum of use to dependence as involving multiple processes and not merely the consequences of graded severity of a single process. However, as Kendler, Aggen, et al. (2012) note, stage-specific predictors of substance use disorders can only be identified in samples that are conditioned on substance exposure because risk for disorder among those who have never been exposed is unknown. Unfortunately, as Kendler, Aggen, et al. (2012) note, the extent of use that is required to create exposure is also unknown.

Finally, in considering risk pathways for substance use disorder, it is important to distinguish between general and substance-specific mechanisms. One consistent finding in the literature is that when multivariate models are fitted to examine common versus unique sources of influence across different drug classes, researchers tend to find evidence for strong common genetic influences and some degree of unique genetic influences on specific drug classes as well (Kendler et al., 2007; Tsuang et al., 1998). These findings tend to be stronger and more consistent when studying phenotypes associated with problems or substance use disorder diagnoses (as opposed to use). As noted earlier, there is substantial co-occurrence of different forms of substance use. Vrieze, Hicks, Iacono, and McGue (2012) created a common factor model of symptoms of nicotine, alcohol, and marijuana abuse using a sample of twins. They found the strongest loadings during adolescence (suggesting that a common factor is more important in adolescence) with weakening into adulthood (suggesting increasing importance of substance-specific influences with age).

Generalized risk pathways that can attempt to explain a broad general liability for substance use disorder focus either on models of the externalizing spectrum or the internalizing spectrum. Externalizing pathways suggest that a heritable predisposition to behavioral undercontrol is central to the development of multiple forms of substance use disorder (Iacono, Malone, & McGue, 2008) whereas internalizing pathways suggest that a common function of substance use is to manage negative affective states, so that substance is maintained or escalated through self-medication of negative affectivity (see Colder, Chassin, Lee, & Villalta, 2010; Hussong, Jones, Stein, Baucom, & Boeding, 2011) or that environmental stress and resulting negative affectivity influence substance use more indirectly by increasing its reinforcement value, the salience of drug-related cues in the environment, or by depleting self-regulatory resources.

However, in addition to models of broad general liability, there are unique genetic effects on regular substance use, alcohol dependence and drug use disorder that are independent of both externalizing and internalizing disorders (e.g., Kendler, Prescott, Myers, & Neale, 2003;

Krueger et al., 2002. This implies that there are also substance-specific pathways. Substance-specific accounts of risk focus on the specific effects of consumption, including the importance of individual differences in positive and negative subjective response (Morean & Corbin, 2008).

Within each of these etiological pathways, it is important to consider gene–environment interplay. This includes gene–environment correlation (rGE) such that individuals with particular genotypes may be exposed to particular environments (passive rGE), may seek out or select particular environments (active rGE), or may provoke particular environmental reactions (evocative rGE, see Jaffee & Price, 2012). It also important to consider gene–environment interaction (GxE), although great caution must be used in interpreting these data because the literature is plagued by failures of replication. When considering GxE interactions in substance use and dependence, we can entertain a range of possible mechanisms including environments that either goad or constrain use (e.g., permissive/facilitative vs. restrictive environments), and thereby facilitate or inhibit use. For example, Stallings et al. (in press) reported that twin studies tend to show higher heritabilities of substance use and other substance-related outcomes in environments characterized by easier access or more permissive attitudes (defined broadly based on religious affiliation, state taxes, school norms) than in environments with less access and less permissiveness. We can also consider environments that alter the individual in some way so that they are more or less internally motivated to use substances (e.g., early trauma leading to negative affectivity and coping motivations) or environments that synergistically interact with drug effects to heighten drug reinforcement (e.g., peer socialization in adolescence; see Sher et al., 2010).

Here we discuss the externalizing, internalizing, and substance use effects pathways in turn. However, it is important to remember that these risk pathways are not necessarily mutually exclusive and, indeed, research supports intersections among them. Moreover, these pathways have been viewed both as etiological models of the development of substance use disorders in general and also as mechanisms for the intergenerational transmission of substance use disorders (i.e., as mediators of the effects of parental substance use disorders on offspring outcomes). Thus, we begin with a discussion of parental substance use disorders as a distal risk factor for the development of substance use disorders in offspring.

Parental Substance Use Disorders

Given the substantial heritability of substance use disorders it is not surprising that substance use disorders run in families and that parental alcohol or drug disorder is associated with increased risk of substance use disorders in the next generation. Adults with a family history of alcoholism are more likely to develop an alcohol disorder (Lieb et al., 2002; Sorensen et al., 2011), with risk ratios ranging between two and three in community samples to nine in severely antisocial samples (McGue, 1994). Parent alcoholism is associated with early onset of alcohol use (Lieb et al., 2002), with greater escalation of substance use over adolescence (Chassin, Curran, Hussong, & Colder, 1996), and a more rapid transition from use to diagnosable disorder (Hussong, Bauer, et al., 2008). The risk associated with parent alcoholism is unique, over and above other parent psychopathology (Chassin, Pitts, DeLucia, & Todd, 1999; Sorensen et al., 2011) although risk for offspring drug disorders is particularly elevated when a biological parent shows both antisocial personality and drug disorder (Langbehn, Cadoret, Caspers, Troughton, & Yucius, 2003). Parental cigarette smoking (particularly trajectories of parental smoking that include early onset, steep escalation, and heavy use) is associated with smoking in the next generation (Chassin et al., 2008; Melchior et al., 2010). Finally, parental drug disorder is associated with increased risk for offspring drug disorders in adolescence (Hoffmann & Cerbone, 2002) and adulthood (Kendler, Sunquist, et al., 2012). Thus, the data are consistent in demonstrating the intergenerational transmission of risk for substance disorders. However, as noted earlier, there are multiple hypothesized biopsychosocial mechanisms underlying this intergenerational transmission including generalized risk for deviant behaviors (the externalizing pathway); generalized risk for internalizing problems (the stress and negative affect pathway); and substance-specific risk in which a history of familial substance disorder is associated with individual differences in the effects of substances. Here we review each of these pathways in turn.

THE EXTERNALIZING PATHWAY

Externalizing problems represent disruptive behaviors such as attention-deficit/hyperactivity disorder (ADHD) symptoms, delinquency, and aggression that bring a child into conflict with others. This domain of childhood behavior problems predicts adolescent substance use and substance use disorders (Hawkins et al., 1992; Zucker, 2006), although these associations are weaker for ADHD than for delinquency and aggression (Lee, Humphreys, Flory, Liu, & Glass, 2011). Moreover, there is a high co-occurrence between antisocial behavior and substance

use disorder (Kendler et al., 2003; Krueger et al., 2002). The strength and robustness of these associations have motivated researchers and behavioral theorists to formulate models of the onset and development of adolescent substance use within the broader context of antisocial behavior (Dishion, Capaldi, & Yoerger, 1999; Dodge et al., 2009; Sher, 1991). The resulting theoretical models overlap with etiological models of antisocial behavior (e.g., Patterson, Capaldi, & Bank, 1991), and integrate a diverse set of risk factors from multiple levels (the individual, family and peer context, schools) into sequential steps such that risk factors build upon each over time on a pathway to substance use. The models start early in life with child characteristics (e.g., temperament traits reflecting behavioral undercontrol and poor self-regulation) and family factors (e.g., parenting) increasing risk for early behavior problems and school difficulties, which in turn, lead to poor social adjustment and affiliation with deviant peers. Deviant peers provide access to drugs and support and reinforce drug use, and are considered to be proximal predictors of substance use. Poor self-regulation or behavioral undercontrol is conceptualized as a core vulnerability that is heritable and shapes and is shaped by the environment (parents, peers, and schools) through reciprocal processes to create a developmental cascade to substance use that gains momentum as children age. The literature documents considerable support for this conceptualization. Below we review the major domains of this developmental cascade, including behavioral undercontrol, parenting, peers, and schools. Finally, we consider the role of genetics and potential gene–environment interactions.

Behavioral Undercontrol

Behavioral undercontrol is an umbrella term that includes externalizing problems, sensation seeking, extraversion, and impulsivity. Traits reflecting behavioral undercontrol are associated with adolescent substance use (Hawkins et al., 1992), and are particularly relevant to the externalizing pathway to adolescent substance use. Individual differences in behavioral undercontrol are evident very early in life (Goldsmith et al., 1987), and poor behavioral control has been shown to predict early emerging externalizing problems in childhood (Shaw, Owens, Giovanneli, & Winslow, 2001), which in turn predict adolescent substance use (Hawkins et al., 1992; King, Iacono, & McGue, 2004). Behavioral undercontrol has been proposed as a core vulnerability that accounts for the developmental continuity between early temperament, externalizing problems, and substance use (Zucker, Heitzeg, & Nigg, 2011). Evidence suggests that the neurocognitive basis for this vulnerability involves the prefrontal cortex and related structures, including the thalamus, basal ganglia, and limbic areas. At the level of behavior, these structures have been described heuristically as reflecting three distinct systems including regulation/control and two motivational/reactive systems that include an approach system and an avoidance system (Nigg, 2000; Putnam, Ellis, & Rothbart, 2001). The control/regulation system is distinguished from the motivational/reactive systems in that the former involves effortful regulation of behavior and the latter involves automatic reactions to novelty, incentives (reward or loss), and threat (Gray & McNaughton, 2000; Putnam et al., 2001). This structural organization is consistent with triadic theories of motivated behavior (e.g., Ernst & Fudge, 2009; Ernst, Pine, & Hardin, 2006). Each of these systems has been linked to substance use in adolescence.

Control/Regulation System

The control/regulation system is controlled by the prefrontal cortex and modulates motivation and reactivity so that an individual can adapt to situational demands in the service of pursuing distal goals. Inhibition of dominant response to engage a subdominant response, planning, error detection, attentional control, and working memory are all involved in control/regulation (Luciana, 2006; Rothbart & Rueda, 2005). There is some evidence that behavior indicative of deficits in these core aspects of control/regulation predict adolescent externalizing behavior and substance use both cross sectionally and longitudinally (Khurana et al., 2013; Zucker et al., 2011). However, links between executive functioning and adolescent substance use have not been supported consistently, and in the externalizing problem behavior domain, links between executive functioning and ADHD are stronger than links between executive functioning and aggression and delinquency (Birkley & Smith, 2011; Castellanos-Ryan, Rubia, & Conrod, 2011; Handley et al., 2011).

The multifaceted nature of the control/regulation system presents a significant challenge to understanding the role it plays in the etiology of adolescent substance use. Although conceptually related, the subdomains of control/regulation (inhibition, planning, error detection, attentional control, and working memory) may not form a unitary construct and some subdomains may be more germane to adolescent substance use than others (Dick et al., 2010). There have been efforts to organize subdomains of control/regulation into a taxonomy or typology (e.g., Nigg, 2000), and such conceptually driven approaches may

help elucidate the role of control/regulation in the etiology adolescent substance use. Another important consideration in understanding the role of the control/regulation system is that it may act as a moderator of motivational/reactive systems. Tripartite models posit that the control/regulation and motivational/reactive systems operate jointly to influence motivated behavior (e.g., Ernst & Fudge, 2009). This implies a moderational model whereby strong motivational/reactive systems that go unchecked by a weak control/regulation system may increase risk for behavioral undercontrol and substance use rather than a weak control/regulation system on its own. Such moderational effects are consistent with dual process models of addiction that posit interactive effects between impulsive or automatic processes and reflective/controlled processes (Gladwin, Figner, Crone, & Wiers, 2011). Dual process models are discussed more fully later when we consider etiological pathways based on substance use effects.

An important caveat in considering the etiological role of the control/regulation system in adolescent substance use is the direction of effects. Imaging studies comparing drug using groups suggest that dysfunction in brain regions associated with memory, working memory, and attention (e.g., decreased hippocampal volume, low prefrontal cortex volume; Squeglia et al., 2009) are associated with heavy alcohol and drug use, even after periods of abstinence. However, most of this research is cross sectional leaving open the question of whether these neural characteristics associated with impaired control/regulation are causes or consequences of drug use. Neuroadaptation to substance use can diminish the capacity of the control/regulation system leading to compulsive drug use (Koob & Volkow, 2010), and the adolescent brain may be particularly vulnerable to the neurotoxic effects of drugs of abuse (Squeglia et al., 2009). Thus, it is possible that a weak control/regulation system increases risk for substance use, but also that drug use further weakens the control/regulation system.

Approach System

The approach system is controlled by the ventral striatum, mediates reactivity to appetitive stimuli, and motivates approach behavior. Evidence suggests that behavioral indices of a strong approach system are associated with externalizing behavior and adolescent substance use (Beauchaine, 2001; Colder & O'Connor, 2004; Knyazev, 2004; Knyazev et al., 2004; Lopez-Vergara et al., 2012). This system has particular relevance to drug addiction given that mechanisms of action of most drugs of abuse involve reward-related brain circuitry (Volkow, Fowler, Wang, & Goldstein, 2002). The intake of many drugs of abuse directly leads to the experience of euphoria, and using drugs because it is fun and exciting is a commonly reported motivation for drug use among adolescents (Kuntsche, Knibbe, Gmel, & Engels, 2005). Adolescents who are characterized by a strong approach system may find the potential euphoria-producing effects of drugs particularly appealing, increasing the likelihood of substance use, and escalation of substance use despite potential negative consequences. In an imaging study, Galvan, Hare, Voss, Glover, and Casey (2007) found that strong activation of the ventral striatum in anticipation of reward was associated with a composite index of risk behavior that included drug and alcohol use. However other studies suggest that *hypoactivation* of the ventral striatum is associated with drug use and behavioral undercontrol (Schneider et al., 2012), suggesting that substance use may be motivated by its ability boost a low hedonic state. Although the underlying neural circuitry remains unclear, motivation for positive arousal mediated by the approach system appears to increase risk for adolescent substance use.

Avoidance System

The avoidance system is controlled by the amygdala, mediates responses to potential aversive outcomes, and motivates reactive inhibition. Activation of the amygdala is involved in conditioned fear and in punishment-motivated learning (Murty, LaBar, & Adcock, 2012). Thus, a weak avoidance system as mediated by amygdala functioning may reduce the impact of potential punishment or aversive consequences on behavior, resulting in unchecked pursuit of reward. Few imaging studies have examined the functional significance of the avoidance system with respect to adolescent substance use, and so we focus our discussion on behavioral studies. Although there is evidence that behavior indicative of a weak avoidance system is associated with childhood externalizing behavior (Beauchaine, 2001), associations with drug use have been inconsistent. Some studies suggest that a strong avoidance system is associated with both low (e.g., Kimbrel, Nelson-Gray, & Mitchell, 2007; O'Connor, Farrow, & Colder, 2008; Simons & Arens, 2007) and high (e.g., Lopez et al., in 2012) levels of substance use. Other studies have shown no association (e.g., Kambouropolous & Staiger, 2007; Knayzev, 2004; O'Connor & Colder, 2005; Voigt et al., 2009).

One explanation for mixed findings regarding the avoidance system and adolescent substance use is that the nature

of the association may depend on age and stage of drug use. With age, substance use becomes increasingly normative (Johnston, O'Malley, Bachman, & Schulenberg, 2012). Early adolescent substance use is part of a broad array of deviant behaviors (e.g., delinquency, violence, sexual promiscuity) that violate age norms in rebellion against authority and rejection of conventional norms (Dishion, Spracklen, Andrews, & Patterson, 1996; Jessor & Jessor, 1977). Youth with a strong avoidance system may be disinclined to engage in such rule violating behavior. Yet, with age, substance use becomes more normative and there is more access to drugs and alcohol and more opportunities to use outside of deviant peer networks (Hussong et al., 2011). Thus, a strong avoidance system may be associated with late age of onset of drug use, and this may appear as a protective effect in early adolescence (or a risk effect associated with a weak avoidance system). However, once initiated, substance use may come to serve as a way of coping with emotional distress associated with a strong avoidance system (e.g., fear and anxiety), resulting in heavy substance use (see our discussion of internalizing or negative affect pathways into drug use). This developmental pattern implies that a weak avoidance system may be associated with substance use in early adolescence, but that a strong avoidance system is associated with heavy problematic levels of substance use at later ages. It is also possible that at later stages (heavy use and disorder), substance use may impact the avoidance system. As noted in our discussion of negative affect pathways, repeated intoxication–withdrawal cycles are thought to activate neural circuits, including amygdala activation, involved in stress responses and drug craving (Kober et al., 2010; Koob & Volkow, 2010) resulting in chronic negative emotional states and motivation to engage in substance use to cope with this distress. In short, a weak avoidance system has strong conceptual links to an externalizing pathway to substance use; however, the role of the avoidance system in the etiology of adolescent substance is complex and remains unclear. Clarifying the role of the avoidance system will likely require considering age and stage of use, as well as distinguishing the avoidance system as cause and effect of substance use.

In sum, there is evidence that the control/regulation, approach, and avoidance systems each affect the phenotypic expression and developmental continuity of behavioral undercontrol. An important consideration for etiological models of adolescent substance use is that neural systems underlying behavioral undercontrol mature in childhood and adolescence. Deficient maturation of the control/regulation system in childhood is thought to foster negative transactions with the social environment and the early emergence of externalizing behavior problems, and thus may play a role in the externalizing pathway to substance use. Moreover, as described earlier, brain maturation that occurs in adolescence, including the disjunction between increases in reward sensitivity/approach system and the slower development of the control/regulation system creates a vulnerability to risk taking that is important in the etiology of substance use.

Early Childhood Development of Behavioral Control

Development of the control/regulation system during the first few years of life is largely mediated by increased efficiency in executive attention, including the ability to inhibit a dominant response and engage a subdominant response, to plan, and to detect errors (Rothbart & Bates, 2006). This development corresponds to normative declines in externalizing behavior that has been documented after the third year of life (Bongers, Koot, van der Ende, & Verhulst, 2004; Colder, Mott, & Berman, 2002). Factors that may impact development of control/regulation in early childhood are of particular relevance to the externalizing pathway to substance use. Prenatal exposure to drugs and alcohol and early life stress are two such factors.

Prenatal Exposure

Maternal substance use has been linked to a range of problems including impaired growth, physical birth defects, behavioral abnormalities, low birth weight, and withdrawal. However, causal relations between fetal exposure and outcomes are difficult to establish because the exposures are nonrandom and the effects are confounded by gene–environment correlation. Moreover, although in the not-so-distant past exposure to illicit drugs received considerable media attention, many of the effects of illegal drugs are time-limited to the neonatal and early childhood period. In contrast, fetal exposure to legal drugs such as tobacco and alcohol appear to be of greater concern to maternal and child health (Chiriboga, 2003).

In terms of maternal smoking, one of its most reliable correlates is low birth weight, an effect that is most associated with maternal smoking during the third-trimester (Reeves & Bernstein, 2008). However, genetically informative studies suggest that the often reported link between externalizing disorders (e.g., ADHD, antisocial behavior) and maternal smoking is a spurious one that is genetically transmitted (Agrawal et al., 2012; D'Onofrio et al., 2008; Langley, Heron, Smith, & Thapar, 2012). For example,

D'Onofrio and colleagues (2007, 2012) compared siblings with differential prenatal exposure to substances on behavioral undercontrol. This quasi-experimental approach controls for a broad range of unmeasured genetic and environmental confounds, and thus provides a rigorous test of prenatal exposure effects on behavioral undercontrol. Findings in these studies supported a causal effect for prenatal exposure to alcohol, but not for tobacco. This suggests that the effects of prenatal exposure to drugs other than alcohol on behavioral undercontrol are likely attributable to genetic risk transmitted from substance using parents or environmentally mediated mechanisms (e.g., caregiving environment; Jaffe, Strait, & Odgers, 2012).

Prenatal alcohol exposure can cause fetal alcohol syndrome (FAS), which is a clinical syndrome characterized by growth retardation, distinct facial dysmorphology, and CNS deficits, including tremors and visual irregularities (Manning & Eugene-Hoyme, 2007). Studies examining school-age outcomes for children affected by FAS reveal a range of cognitive and behavioral problems that often persist or worsen as children mature, leading to high rates of antisocial behavior and the development of AUDs (Baer, Sampson, Barr, Connor, & Streissguth, 2003). These types of deficits and associated behavior problems are also common in children prenatally exposed to alcohol who are not diagnosed with full-syndrome FAS (Testa, Quigley, & Eiden, 2003) but have some subsyndromal spectrum disorder. Animal models suggest that fetal exposure to alcohol may lead to the development of specific drug sensitivities and preferences that may contribute to the development of AUDs (Valenzuela, Morton, Diaz, & Topper, 2012).

Although the evidence is strong for a causal effect of prenatal alcohol exposure on behavioral undercontrol, there is uncertainty about what levels of alcohol exposure confer risk to the developing fetus and whether vulnerability varies across different periods of pregnancy. Nonetheless, the most consequential effects of prenatal exposure to alcohol are on brain development, which in turn, impacts cognitive and behavioral functioning (Mattson & Riley, 1998). The specific mechanisms through which prenatal alcohol exposure operates are unclear in part because of the broad range of effects of ethanol on brain systems. Evidence from animal models suggests that prenatal exposure to drugs or alcohol impacts reward neural circuitry of the approach system (Malanga & Kosofsky, 2003), but this work has not been extended to humans. Human imaging studies suggest that prenatal alcohol exposure is associated with reduction and thinning of brain structures germane to the control/regulation system (Riley & McGee, 2005).

Early Childhood Adversity

Early childhood adversity, including child abuse and maltreatment, exposure to violence, and parental loss, is also associated with childhood externalizing behavior problems and with increased risk for adolescent drug use, and likely influences the externalizing pathway through multiple mechanisms. The most profound of these mechanisms involves detrimental effects on neural development and brain systems (Champagne, 2010) that influence stress reactivity, the approach system, and the control/regulation system (Andersen & Teicher, 2009). Early adversity enhances stress reactivity through changes in the hypothalamus-pituitary-adrenal (HPA) axis, which in turn, increases reactivity to drugs of abuse, drug sensitization, and stress induced reinstatement of extinguished drug use. However, increased stress reactivity effects are likely specific to drug use rather than broadly germane to behavioral undercontrol as the link between functioning of the HPA axis and behaviors indicative of behavioral undercontrol other than substance use has not been consistently shown (Marsman et al., 2008). Thus, although stress reactivity as mediated through the HPA axis is important for the etiology of addictive behaviors, it may not be specific to the externalizing pathway (see our discussion of internalizing pathways). More germane to the externalizing pathway are the effects of early adversity on dampening activity of the approach system (Matthews & Robbins, 2003) that may motivate undercontrolled behavior to increase low arousal, and reduced volume of the prefrontal cortex, a region central the control/regulation system (Arnsten, 2009) that may impair capacity for self-regulation.

Parenting

Parenting reflects both goal directed behaviors that parents use to socialize their children (e.g., discipline and monitoring) and nongoal-directed behaviors that create an emotional climate (e.g., warmth), and has long been considered an important influence on child adjustment outcomes. There is considerable evidence from longitudinal correlational studies that parenting exerts an influence during early childhood and through adolescence, and that similar parenting behaviors impact externalizing behavior problems and substance use (Barnes, Reifman, Farrell, & Dintcheff, 2000; Loeber & Stouthamer-Loeber, 1986). Further support for parenting effects is gleaned from intervention studies that show that changes in parenting mediate intervention effects on externalizing problems and substance use (Brody et al. 2004; Sandler et al., 2011). There is also evidence that parenting changes as children

age, and hence, it is important to consider the different role that parenting may play in early childhood versus adolescence.

Early Childhood

Inconsistent use of discipline, failure to use positive parenting strategies, low responsiveness (including neglect), and excessive use of harsh discipline (including abuse) are associated with childhood externalizing problems (e.g., conduct disorder, delinquency, and aggression; Rothbaum & Weisz, 1994). Although parenting is often assumed to influence child behavior, there is evidence for a transactional process whereby child behavior elicits parental reactions, which in turn, influence child behavior (Bell & Chapman, 1986). Patterson and colleagues have accumulated substantial support for a coercive parent–child exchanges that inadvertently reinforce and escalate disruptive behavior (Patterson, Reid, & Dishion, 1992). Transactional processes between parent and child start very early, suggesting that risk for the externalizing pathway to substance use is apparent many years prior to initiation of substance use. Children with difficult temperaments are difficult to manage and they elicit more control and negativity, less responsiveness, and rejection from parents in infancy and toddlerhood, and these parenting behaviors have the effect of exacerbating the child's difficult temperament (Kiff, Lengua, & Zalewski, 2011). Moreover, child traits reflecting behavioral undercontrol are more strongly associated with externalizing behavior problems when parenting is negative and harsh (Kiff et al., 2011; Rothbart & Bates, 2006). This supports the notion that phenotypic continuity in behavioral undercontrol is most evident in the context of poor parenting.

Many of the same parenting behaviors that predict childhood externalizing problems also predict adolescent substance use. For example, Dishion, Capaldi, & Younger (1999) found that harsh and inconsistent discipline assessed at age 9 predicted substance use at age 15. Positive parenting (e.g., discipline characterized by reasoning and discussion, and proactive family management) in early childhood protects youth from adolescent substance use (Kaplow, Curran, Dodge, & the Conduct Problems Prevention Research Group, 2002; Kosterman, Hawkins, Guo, Catalano, & Abbott, 2000). Lack of parental warmth and involvement in early childhood has also been shown to predict adolescent substance use (Kaplow et al., 2002; Shedler & Block, 1990). At least some of the effects of early parenting on adolescent substance use are mediated through externalizing behavior problems (Dodge et al., 2009). Taken together these findings suggest that early transactional processes between a difficult to manage child and poor parenting lead to the emergence of externalizing behavior, and subsequently substance use. Later in this section we discuss one of the key mechanisms by which externalizing problems lead to drug use, namely affiliation with peers who provide access to and reinforcement for drug use.

Adolescence

Developmental changes of adolescence shift the nature of parent–child interactions and parenting. In general, parents grant their children more autonomy in adolescence, and some transient reductions in parent–child closeness in early adolescence are most likely to be manifested in increased privacy on the part of the adolescent (Steinberg & Silk, 2002).

With the transition into adolescence, parenting continues to influence risk for substance use, but the relevant parenting domains include increased importance of supervision and monitoring as adolescents spend increased amounts of time in peer contexts outside of parents' presence. Several studies have found that low levels of parental monitoring and supervision predict adolescent substance use (Barnes et al., 2000; Chilcoat & Anthony, 1996; Dishion, Capaldi, Spracklen, & Li, 1995) as well as adolescent externalizing behavior (Dishion & McMahon, 1998). As in early childhood, longitudinal studies suggest reciprocal associations, such that low levels of parental monitoring/supervision predict high levels of adolescent substance use and externalizing behavior, and high levels of externalizing behavior predict low levels of monitoring (Kerr & Stattin, 2003; Laird, Pettit, Bates, & Dodge, 2003). Thus, although monitoring/supervision may play a role in controlling exposure to a risky ecological context, when youth engage in problem behavior and substance use, this can degrade parental monitoring. The mechanisms for this effect are not clear. One possibility is that when adolescents engage in problem behavior, parent–child communication decreases (Dishion, Poulin, & Medici Skaggs, 2000), perhaps reflecting the adolescent's effort to undermine parental monitoring (Stoolmiller, 1994). Evidence suggests that adolescent disclosure is the primary means by which parents obtain knowledge about their child's activities and whereabouts (Kerr & Stattin, 2000). Therefore, declines in communication may result in less effective monitoring.

Parenting reflecting positive parent–child relationship quality (high levels of parental warmth and involvement, high levels of social support, closeness) is associated with

lowered risk for adolescent substance use (Ellickson, Perlman, & Klein, 2003; Hawkins et al., 1992). Parent–child relationship quality has been conceptualized as part of a dynamic model that includes parental monitoring and discipline (Dishion & McMahon, 1998). Positive parent–child relationships enhance and motivate effective discipline and monitoring and effective parenting practices nurture positive relationships. Indeed, psychometric work suggests relationship quality, monitoring, and discipline are highly related constructs (Dishion, Li, et al. 1999; Patterson et al., 1992), and some work suggests that relationship quality predicts the effective monitoring (Barnes et al., 2000). Thus, although monitoring and supervision are important influences of adolescent substance use, it is likely that this domain of parenting does not operate alone, and it is important to consider potential dynamic associations between multiple domains of parenting.

There is also evidence that substance use-specific parenting is associated with adolescent substance use. Discussing risks of drug and alcohol use, maintaining restrictive rules about use, implementing punishments for use, and communicating disapproval of use are associated with lowered risk for adolescent substance use (Chassin, Presson, Todd, Rose, & Sherman, 1998; Henriksen & Jackson 1998; Kodl & Mermelstein, 2004; Martino, Ellickson, & McCaffrey, 2009). However, these effects are not consistently found and the field is limited by an over-reliance on questionnaire methods rather than direct observations of interactions (see Wakschlag et al., 2011, for an exception). The effects of substance use specific parenting have been weaker for parents who themselves use substances and stronger in adolescent reports than in parent reports (Chassin et al., 2005). Moreover, some parental attempts at substance-specific parenting are associated with increased adolescent use and, as with general parenting, the relations between substance-specific parenting and adolescent substance use are likely bi-directional (Huver, Engels, & de Vries, 2006).

Although the association between parenting and adolescent externalizing behavior and substance use is often attributed to environmental effects (e.g., the influence of parenting or reciprocal influences between parenting and adolescent behavior), there is evidence that some of this association may be genetically influenced, particularly in adolescence. Heritability of behavior increases from childhood to adulthood in a variety of domains, including family relationships (Bergen, Gardner, & Kendler, 2007). Using a longitudinal twin design that followed youth from age 11 to 17 years, Ludeke, Johnson, McGue, and Iacono (2013) found that genetic influences on quality of the parent–child relationship increased over time. Moreover, initial levels of genetic influence at age 11 were positively associated with increases in genetic influence. This suggests "amplification" of genetic influence as youth age into adolescence.

Peers and School Failure

Adolescent substance use largely takes place in the context of peers, and considerable evidence supports affiliation with deviant peers as an important proximal influence that promotes substance use (Chuang, Ennett, Bauman, & Foshee, 2005; Fergusson, Boden, & Horwood, 2008). One mechanism leading to affiliation with deviant peers is rejection from mainstream peer groups and peer rejection in childhood has been linked to later substance use (Dishion et al., 1995; Kaplow et al., 2002). Behaviorally undercontrolled and aggressive youth are at risk for peer rejection (Dodge et al., 2003), and rejected youth tend to gravitate toward similarly undercontrolled and rejected peers who are likely to be accepting of deviant behavior (Coie, 1990). Affiliating with deviant peers not only provides opportunities for reinforcement of deviant behavior, and but also missed opportunities to be socialized by prosocial youth. Taken together, these findings suggest that a high risk temperament, characterized by behavioral undercontrol, creates a vulnerability for early social experiences with peers that can push a child further along on the externalizing pathway to substance use.

As with peer rejection, school failure may similarly push a child further along the externalizing pathway by strengthening affiliation with deviant peers. Children who are behaviorally undercontrolled are at increased risk for school failure (Patterson, 1986). Poor grades, low educational aspirations, and low connectedness to school, and low expectation for academic success increase risk for alcohol and drug use (Bond et al., 2007; Cox, Zhang, Johnson, & Bender, 2007). Difficulties in school are thought to lead to negative labeling, rejection by prosocial peers, rejection of school, and affiliation with deviant peers who similarly reject school. In support of this notion, school difficulties predict affiliation with deviant peers (Dishion, Patterson, Stoolmiller, & Skinner, 1991; Simons, Whitbeck, Conger, & Conger, 1991). Although deviant peer groups in childhood rarely engage in substance use, they become an important context of drug and alcohol use in adolescence.

Deviant peers support an array of behaviors that violate age norms in rebellion against authority and rejection of conventional norms (Dishion et al., 1996; Jessor & Jessor, 1977). In adolescence, deviant peers provide support and

opportunities to engage in alcohol and drug use, increase the perception that use is normative, socially reinforce use, and shape attitudes favorable toward drugs and alcohol (e.g., Prinstein & Wang, 2005). A number of studies have found that adolescent substance use is predicted from that of their friends (Hawkins et al., 1992) and that these associations are evident even when peers report on their own substance use (Kandel, 1978). Moreover, the presence of nondrug-using peers in one peer context (e.g., within a close friendship group) can offset risk in another context (e.g., within a larger peer group, Hussong & Hicks, 2003).

In a recent review, Neisewander, Peartree, and Pentwoski (2012) suggested that the social and pharmacological rewards of drug use may interact synergistically to produce a more rewarding experience than either type of reward alone. They posited two neurobehavioral mechanisms for such an effect. One mechanism involves shifting the salience of incentives (either decreasing salience of aversive consequence of drug use or increasing salience of rewarding stimuli), and the other mechanism involves a drug acquiring conditioned reinforcing effects by being paired with social reinforcers. These ideas remain to be tested, but they may have particular relevance for considering the role of peer influence on adolescent drug use. Relative to children and adults, adolescents are more responsive to social stimuli, and this may be attributable to biological aspects of pubertal maturation (e.g., a proliferation of oxytocin receptors) that affect social bonding and recognition and memory of social stimuli (Steinberg, 2008). Hence, increased salience of peer relationships and social reinforcement may render adolescents particularly vulnerable to hypothesized synergistic interactions between social and drug reward. Indeed, for adolescents, the presence of peers itself activates the same reward centers that lead to risky behavior (Chein, Albert, O'Brien, Uckert, & Steinberg, 2012).

Although peer effects are most often conceptualized as social influences, there is also substantial support for peer selection effects (Burk, van der Vorst, Kerr, & Stattin, 2012; Dishion & OwEn, 2002; Go, Green, Kennedy, Pollard, & Tucker, 2010; Schaefer, Hass, & Bishop, 2012). These selection effects suggest that individuals seek to affiliate with others who are behaviorally similar to themselves (Kandel, Davies, & Baydar, 1990). Thus, adolescents with an interest in or desire to use drugs and alcohol tend to select peers with similar predilections. Fowler et al. (2007) found that twin reports of peers' substance use were largely explained by genetic influences, suggesting a genetic influence on peer selection. Genetic influences on peer selection were also reported by Cleveland, Wiebe, & Rowe, (2005) and Hill, Emery, Harden, Mendle, & Turkheimer (2008). However, peers further influence substance use outcomes over and above genetically mediated peer selection effects (Chassin et al., 2012; Harden, Hill, Turkheimer, & Emery, 2008). Thus, peer influences may serve to mediate the effects of genetic risk on alcohol outcomes. There is also support for interactions between genetic risk and peer influences. For example, Harden et al., (2008) found that adolescents who were genetically at risk for alcohol and tobacco use were also the most vulnerable to influences from their closest friends.

Gene–Environment Interplay and the Externalizing Pathway

Behavioral genetic studies suggest that both genetic and environmental (shared and nonshared) influences are important for adolescent substance use (Hopfer et al., 2003). As noted earlier, there is stronger genetic risk at later ages and for later stages of substance use. Genetic risk may be particularly important for the externalizing pathway because behavioral undercontrol has been viewed as the common heritable characteristic that underlies use of different substances as well as developmental continuity of early indicators of externalizing problems and later substance use (Iacono et al., 2008; McGue, Iacono, & Krueger, 2006; Korhonen et al., 2012). Several studies have proposed candidate genes relevant to adolescent substance use that are also germane to behavioral undercontrol, including the MAO-A gene (Nilsson, Wargelius, Sjöberg, Leppert, & Oreland, 2008), genes involving the serotonin transporter (Nilsson et al., 2005), dopamine genes (Derringer et al., 2010), and variants of the GABRA2 gene (Dick & Mustanski, 2006; Dick et al., 2013). These candidate genes seem to play a role in modulating neural reward circuitry and the capacity to inhibit behavior, and thus influence the strength and functioning of the approach, avoidance, and control systems described above. However, the functional significance of genetic risk for neurobehavioral mechanisms of substance use is not well understood (Agrawal et al., 2012). Studies that integrate neuroimaging and genetic approaches offer the opportunity to examine such mechanisms, yet few studies to date have done so (Karoly, Harlaar, & Hutchison, 2013), particularly with adolescent samples. Understanding the mechanisms of genetic risk will have important implications for treatment and prevention, and this is an important direction for future research.

In general, findings from genetic studies of adolescent substance use echo the conclusions from adult studies

(Lessov, Swan, Ring, Khroyan, & Lerman, 2004) that although heritable factors are important, there are also important environmental influences. Hence, adolescent substance use is thought to arise from complex interplay between genes and the environment, which have been studied as gene x environment interactions and (less frequently) as gene–environment correlations. Some candidate gene studies indicate that environmental factors that are involved in the externalizing pathway, moderate genetic risk for substance use. The most commonly examined environment factor in these studies has been parenting. For example, parental supervision and involvement have been found to reduce risk for adolescent substance use that was associated with the MET allele of the catechol-O-methyltransferase Val158 Met genotype, (Laucht et al., 2011) and the 5-HTTLPR polymorphism (Brody et al., 2009). Parental rule setting reduced the risk for adolescent alcohol use that is associated with the TAQA1 genotype (van der Zwaluw et al., 2010), although this genotype did not show differential effects as a function of parent rejection, overprotection, or warmth (Creemers et al., 2011). Although Dick et al. (2007) did not examine candidate genes, their twin study suggested that high levels of parental monitoring reduced genetic risk for adolescent smoking. These findings parallel those discussed earlier, namely that an early high risk temperament is more likely to predict later externalizing problems in the context of poor parenting (Kiff et al., 2011; Rothbart & Bates, 2006). Thus, there is converging evidence suggesting phenotypic continuity of behavioral undercontrol is more likely in the context of poor parenting. Other studies have found that religiosity, family functioning, and high risk contexts (e.g., the presence of adults who model use and easy access to substances) moderate genetic risk for adolescent substance use (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001; Nilsson et al., 2005; Timberlake et al., 2006); However, as noted earlier, gene–environment interactions in the candidate gene literature have been limited by failures to replicate (Duncan & Keller, 2011). Statistical interactions are notoriously difficult to detect in the behavioral sciences, largely due to small effect sizes and unreliability of measurement (McClelland & Judd, 1993). Several methodological refinements that might help advance research on gene x environment interactions include limiting consideration to those genetic variants that are linked to a relevant phenotype and moving away from candidate genes to considering aggregate genetic variants (Vrieze, McGue, Miller, Hicks, & Iacono, 2013).

As noted earlier, according to transactional models, a child's behavioral undercontrol may evoke negative responses from others (rejection from peers, poor parenting), which may shape the social context that the child experiences (e.g., selection into deviant peer groups). If the child's behavioral undercontrol is genetically influenced, then such a process would be evident in gene–environment associations (Hicks et al., 2013). Using a twin design, Hicks et al. (2013) found that externalizing problems at age 11 predicted contextual risk (a composite of deviant peer affiliations, low quality parent–child relationship, and school difficulties) at age 14, which in turn predicted substance use at age 17. Importantly, although early externalizing problems were attributable to both environmental (shared environment) and genetic influences, contextual risk mediated most of the genetic influence of early externalizing problems on later substance use. Thus, environmental influences can mediate the effect of genetic risk on substance use outcomes (Jaffee & Price, 2012).

THE INTERNALIZING PATHWAY

Although less often the focus of study than the externalizing pathway, the internalizing pathway and related negative affect models are often implicated in the etiology of drug use and disorder (Colder et al., 2010; Kassel et al., 2010; Mayes & Suchman, 2006). Research regarding the association between drug use disorders and negative affect-related disorders, like major depressive disorder, bipolar disorder and the anxiety disorders, has a long history in the epidemiological and clinical literatures (see Babor, 1996; Zucker, 2006). This research maps onto perceptions by individuals who abuse drugs that negative emotions play a key role in drug use (and vice versa; Stopka, Springer, Khoshnood, Shaw, & Singer, 2004) and that coping motives are a primary reason for drug use particularly in treatment-seeking populations (Bizzarri et al., 2007). However, developmentally informed research regarding the association between negative affect and drug use disorders is a more recent addition to this literature (Hussong et al., 2011; Masten, Faden, Zucker, & Spear, 2009; Zucker, Donovan, Masten, Mattson, & Moss, 2008).

The most frequently cited term used to describe the mechanism underlying associations between negative affect and substance use is self-medication. This lay term, however, does not have a precise definition in the scientific literature and may indeed encompass several different mechanisms (see Kassel et al., 2010). For that reason, we avoid using this overarching term to focus instead on prominent mechanisms purported to underlie negative affect–drug use associations. The first of these is the classic

negative reinforcement model (e.g., Jellinek, 1960; Wikler, 1948). This model has been offered to explain drug use as a motivated behavior with the goal of alleviating or avoiding negative affect. The model has been used to describe motives for drug use (broadly) as well as for the maintenance of established drug using patterns and addiction (more specifically). In a reformulation of the negative reinforcement model, Baker and colleagues (Baker et al., 2004; McCarthy, Curtin, Piper, & Baker, 2010) acknowledge that alleviating or avoiding negative affect remains a primary motive for drug use. However, their reformulation emphasizes interoceptive cues that signal impending negative affect associated with withdrawal symptoms as the salient conditioned stimuli prompting drug use. Through repeated pairing of these interoceptive cues (e.g., lessening of either the "throat scratch" sensation or the paralysis of pulmonary cilia associated with falling nicotine levels in the blood) with subsequent negative affect, individuals learn to detect interoceptive cues as a prompt for the use of drugs to avoid negative affect associated with the withdrawal process. Importantly, drug use conditioned on interoceptive cues may occur even before conscious awareness of negative affect. Moreover, this withdrawal-relief pairing may generalize beyond withdrawal-based negative affect to motivate drug use in response to negative affect more generally (i.e., that is not prompted by drug withdrawal) because interoceptive cues become a conditioned stimuli prompting drug use that is no longer linked directly to the source of negative affect (i.e., withdrawal versus environmental sources). The extent to which drug-induced negative affect (e.g., cocaine-induced anxiety) may occur and signal risk for relapse may depend on underlying neurobiological mediators (e.g., evidence of norepinephrine signaling in beta-adrenergic receptors; Ashton-Jones & Kalivas, 2008; Schank, Liles, & Weinshenker, 2008). Thus, negative reinforcement models may be used to explain associations between experienced negative affect and drug use as well as between conditioned precursors to negative affect and drug use.

However, negative reinforcement models are not the only mechanisms posited to underlie associations between negative affect and drug use. For example, Kaplan's (1980) self-derogation theory posits that negative affect, or distress associated more specifically with social rejection, may lead to social drift in which rejected adolescents find acceptance with nonmainstream, deviant youth. Entry into this group may serve to decrease distress, but also to increase risk for engaging in deviant behavior that is modeled and reinforced by this peer group. In contrast to the direct effect of negative affect (and antecedent interoceptive cues) on drug use posited by the negative reinforcement models, self-derogation theory posits indirect effects in which social affiliations serve to mediate the association between negative affect and drug use. Thus, affiliation with substance use-promoting peers may be a common proximal mediator for both internalizing and externalizing pathways to the development of substance use disorders.

A third model regarding the role of negative affect in drug use compares the ability to self-regulate actions and emotions, such as negative affect, to the use of a muscle (Baumeister, 2003). In this model, the ability to regulate affect, and supposedly to then avoid prolonged states of negative affect, is seen as requiring the expenditure of a limited resource. To the extent that intense effort to self-regulate has recently been expended, available responses will be depleted to respond to a new stressor or demand requiring self-regulation. Individuals with depleted resources, or ego depletion, are then viewed as vulnerable to engaging in deleterious behaviors, such as drug use, to cope with or avoid negative affect given a lack of resources to stop the impulse to use drugs in this way. Evidence supporting this model comes from lab studies in which male social drinkers drank more after exerting self-control in a stress task than those not subjected to this task (Muraven, Collins, & Neinhaus, 2002).

A fourth model of the role of negative affect is particularly relevant once drug use patterns have been established. That is, negative affect may serve to increase the reward value of drugs and to draw attention to drug cues in the environment and increase the likelihood of relapse. For example, Tull, McDermott, Gratz, Cofey, and Lejuez (2011) showed that exposure to a trauma script among cocaine-dependent inpatients resulted in increased attention to cocaine imagery among those with a post-traumatic stress disorder versus those without. Moreover, imaging studies implicate functioning in the anterior cingulate cortex (Goldstein et al., 2009) in increased sensitivity to cocaine cues and use following emotionally salient tasks and animal models indicate that the strength of this sensitivity is influenced by genetic liabilities (e.g., Ofil1 and Ofil2 on chromosomes 4 and 7 as related to stress responsivity in selectively bred strains; Vendruscolo et al., 2009).

These multiple negative affect mechanisms of drug use underscore the potential complexities that may underlie a cyclical, bi-directional association between negative affect and drug use. In addition, these negative affect models of drug use are clearly not mutually exclusive. They suggest that negative affect may play several different roles in the development of drug use. And several of them emphasize the role of negative affect as either solely occurring in

(or most evident in) the maintenance and escalation of drug use as opposed to initiation and experimental use. Nonetheless, they all suggest that negative affect may play a role that increases the likelihood of subsequent episodes of drug use.

THE NEGATIVE AFFECT–DRUG USE RELATION

A fundamental question common to all variants of negative affect models of drug use is whether there is empirical evidence for an association between negative affect and drug use disorders such that negative affect signals risk for later drug use and disorder. Surprisingly, the current literature does not offer a clear answer to this most basic question, a likely reason for the relatively lower emphasis on internalizing versus externalizing pathway models for drug use and disorder (Hussong et al., 2011).

Epidemiological studies show substantial comorbidity of negative affect-related disorders and drug use disorders (Grant, 1995; Kessler et al., 1996, 2001; Merikangas et al., 1998). For example, in an analysis of the nationally representative NESARC sample of 43,093 adults aged 18 years and over, Conway, Compton, Stinson, and Grant (2006) found clear evidence for negative affect–drug use associations. In these findings, the association between mood disorders and drug dependence (OR = 7.1) was greater than that between mood disorders and drug abuse (OR = 2.3), with a similar though dampened pattern for anxiety disorders (OR = 4.9 with drug dependence and 1.7 with drug abuse). Among those with any drug use disorder, 40.9% met criteria for a mood disorder and 29.9% did so for an anxiety disorder as compared with 19.5% and 16.2% of respondents with these disorders in the sample at large. Similar support for negative affect–drug use associations also appears in studies of adolescents. In the nationally representative MECA study, Kandel et al. (1997) report rates of anxiety and mood disorders of over 30% and 24%, respectively, for adolescents who used illicit drugs in the past year as compared with 12% and 6%, respectively, for those who had not.

Thus, the negative affect–drug use association appears well supported (although not universally so; see King & Chassin, 2008; Woiltzky-Taylor et al., 2012); more controversial is the question of directionality. Many negative affect models of drug use posit that negative affect is a precursor to drug use, though most acknowledge the bidirectionality of this association. (We defer consideration of the etiological role of drug effects for a subsequent section). Most existing epidemiological studies, however, either test the association between negative affect and drug use disorders cross sectionally or using retrospective recall (Conway et al., 2006). In their review of the literature, Degenhardt, Hall, and Lynskey (2003) reported that longitudinal studies find little evidence that depression increases risk for later marijuana abuse in community samples, and mixed support for increased depression following periods of heavy cannabis use. In contrast, other longitudinal studies show prospective prediction of polydrug use from adolescent depression (Bardone, Moffitt, Caspi, Dickson, & Silva, 1996), that depression and anxiety in childhood predict later drug use disorders in adolescence (Reinherz, Giaconia, Hauf, Wasserman, & Paradis, 2000) and that anxiety disorders in adults predict increased incidence of drug use disorders one year later (Robinson, Sareen, Cox, & Bolton, 2011). These studies may indicate that directionality for negative affect models of drug use is drug specific. However, longitudinal studies reporting these associations remain sparse for specific drugs of abuse and underpowered for these low base rate behaviors, suggesting that conclusions regarding directionality may be premature.

In addition to questions about directionality, epidemiological studies of comorbid affect-related disorders and drug use disorders have been criticized for not taking into account significant confounding factors. These include co-occurring use of alcohol and tobacco (Degenhardt et al., 2003) as well as antisociality, deviance, and externalizing symptoms (Colder, Scalco, et al., 2012; King & Chassin, 2008). Among adolescents, effects of internalizing symptoms on drug use are significantly diminished, only present in subgroups or sometimes absent after controlling for co-occurring externalizing symptoms (Kassel et al., 2010; Mason, Hitchings, & Spoth, 2007; McCarty et al., 2012; Oshri, Rogosch, Burnette, & Cicchetti, 2011). For example, in a community sample of young adolescents, externalizing symptoms in the absence of internalizing symptoms were strongly associated with marijuana use whereas co-occurring internalizing and externalizing problems were weakly associated with prospective substance use and internalizing symptoms alone were protective against later marijuana use (Colder, Scalco, et al., 2012). Given this pattern of findings and the high co-occurrence of internalizing and externalizing symptoms (Angold, Costello, & Erkanli, 1999; Lewinsohn, Shankman, Gau, & Klein, 2004), studies that examine the unique effects of internalizing symptoms in predicting drug use after controlling for externalizing symptoms are particularly informative, though rare in the literature. The current epidemiological literature thus establishes a strong association between

negative affect and drug use disorders, though the nature and uniqueness of this association remains unclear.

Importantly, even multiyear longitudinal studies may miss the time-window in which negative affect–drug use associations unfold, such that the time intervals between assessments are not well matched to the temporal relations between negative affect and drug use. Moreover, many of these studies make between-person comparisons to draw time-specific conclusions. That is, analyses test whether individuals with greater emotional distress are more likely to use drugs as compared with individuals with lower emotional distress rather than testing within-person comparisons that ask whether individuals are more likely to use drugs at those points in time when they are more distressed compared with those points in time when they are less distressed. This distinction between person- and time-specific comparisons is particularly important in the study of negative affect models of drug use because these comparisons map onto different mechanisms that may account for negative affect–drug use associations. By distinguishing person- and time-specific mechanisms that explain this association on both theoretical and analytical levels, we move the question of interest from whether these two constructs are associated to how these two constructs might be associated. Given existing complexity in the epidemiological literature, this change in focus may prove especially fruitful.

Methods that are well suited to the task of parsing person- and time-specific processes occurring on a micro time scale are daily assessment designs, such as daily diary methods, ecological momentary analysis, and experience sampling methods. Although still an underutilized technique, these studies show some evidence that negative affect signals risk for substance use in select youth (Hersh & Hussong, 2009; Hussong, Feagans Gould, & Hersh, 2008). Daily assessment designs are also increasingly being used to differentiate person- and time-specific mechanisms underlying risk for relapse among individuals receiving treatment (Shiffman, 2009). These daily assessment studies are used to capture the immediate internal experiences and external situational factors surrounding drug use as well as the acute effects of drugs and dynamic processes underlying mood-use associations. These techniques are most well developed for studies of adult alcohol and tobacco use (Shiffman, 2009), and some reservations have been raised about their feasibility with illicit drug using populations (Palij, Rosenblum, & Magura, 2003). However, work by Epstein and colleagues demonstrate that such methods may yield rich findings about illicit drug use with implications for treatment and intervention.

Participants in the Epstein studies were cocaine- and heroin-using outpatients enrolled in a methadone treatment program who responded to multiple random and event-contingent prompts to complete a 5-week intensive assessment period (5 + times per day) followed by a 20-week less intensive assessment period (2 + times per day) using PDAs. Of the 114 participants enrolled in the study, 102 participants completed an average of 75% of prompted assessments regarding drug use and craving, ranging from 22–98% per participant, with reports capturing over 4,000 assessments of drug use or craving. Importantly, a key finding of this study is that daily assessment designs with drug using samples are not only feasible, but they can also capture significant rates of craving and drug use. Analyses of concurrent mood and drug use/craving reports in these data indicated that good moods were associated with cocaine use whereas feelings of sadness or anger were associated with heroin use (Epstein et al., 2009). Similar within-day associations based on concurrent mood and use/craving assessments were also found by Cleveland and Harris (2010) in a small sample of participants drawn from a collegiate recovery community. However, other findings indicate that this essentially cross sectional finding may mask greater complexity in the time-specific mood-use/craving association. For example, hourly assessments of mood occurring within 5 hours before craving/use events showed only weak prospective associations between mood and cocaine use/craving in analyses of the Epstein and colleagues sample (Preston & Epstein, 2011). In addition, Buckner et al. (2011) found that daily mood ratings played a complicated role in moderating craving-use associations, such that predictions of anxiety sensitivity in the moment served to increase the likelihood that cravings to use marijuana predicted subsequent marijuana use. As with studies of alcohol and tobacco use, these findings provide initial evidence that mood-use/craving associations may be more complex than simple main effect predictions drawn from classic negative reinforcement models. Rather, the extent to which negative mood may serve as a signal is likely moderated by a host of other factors, as appears to be the case for alcohol use (Hussong, Hicks, Levy, & Curran, 2001; Cooper, Russell, Skinner, Frone, & Mudar 1992). Experience sampling and ecological momentary methods are one set of tools for testing such models.

In sum, strong evidence for comorbidity between negative affect-related disorders and drug use disorders has led to an emerging body of research seeking to understand the mechanisms that underlie this comorbidity. Although studies of negative affect models of illicit drug

use have lagged behind those for alcohol and tobacco use, the emerging evidence yields findings open to multiple and sometimes conflicting interpretations. To reconcile these interpretations of the literature, more complex negative affect models of drug use and disorder are needed that acknowledge (1) that several different mechanisms may underlie the association between negative affect and drug use; (2) that each mechanism may require a unique methodology to optimally test and differentiate which mechanisms are most likely to account for this association; and (3) that negative affect models may only explain drug use and disorder for a vulnerable subset of the population or within certain circumstances (Hussong et al., 2011; Zucker, 2008). Moreover, these affect-related mechanisms may (4) be differentially able to account for substance use onset, escalation, recovery and relapse; (5) differ in their applicability to substance use across different stages of the life course; and (6) may depend on the drug of abuse and form of affect under consideration. Few studies account for more than one or two of these many points of potential variation in the association between negative affect and drug use. For that reason, unaccounted for differences in samples and methodologies may be in part responsible for the disparate findings comprising this literature. However, as with any emerging process, understanding drug use and disorder from a developmental psychopathology perspective will require the consideration of mechanisms, methods matched to test those mechanisms, and more complex theoretical models to account for what is likely to be a dynamic relation between negative affect and drug use over ontogeny.

AN INTERNALIZING DEVELOPMENTAL PATHWAY

Current negative affect models of drug use largely lack a developmental perspective and none take into account developmental processes that precede adolescence. Filling this gap in the literature, is a proposed internalizing pathway to substance use and disorder that consolidates existing studies into a theoretical model positing an early emerging risk for substance use and disorder (Hussong et al., 2011). Although most relevant literature regarding this pathway focuses on alcohol use outcomes, some evidence indicates that the internalizing pathway likely also predicts drug use and disorder more broadly. This pathway posits that core deficits that drive substance-using behaviors may be heterogeneous across drug using populations, with one subgroup abusing substances as a manifestation of an underlying deficit in emotion regulation.

Some evidence for a unique core deficit underlying negative affect-related disorders and drug use disorders comes from behavioral genetic studies, an active area of study. Currently, family linkage and twin studies demonstrate modest co-transmission for internalizing disorders (primarily depression) and alcoholism in adult samples (Kendler, Neale, Heath, & Kessler, & Eaves, 1994; Merikangas, Leckman, Prusoff, Pauls, & Weissman, 1985; Zucker, 2006). Moreover, Silberg, Rutter, D'Onofrio, and Eaves (2003) report findings from a multivariate behavioral genetic analysis that genetic influences played a greater role in the comorbidity of depression and drug use in girls versus boys, though substantial environmental variance was found for both sexes. In addition, summarizing results from the Collaborative Study on the Genetics of Alcoholism, Nurnberger, Foroud, Flury, Meyer, and Wiegand (2002) reported evidence consistent with examining Negative Affect Alcoholism as a unique phenotype. Specifically, they report a higher rate of comorbid depression and alcoholism among probands of families with a higher prevalence of this same comorbidity as opposed to families with a higher prevalence of alcoholism alone. This finding spurred genetic analyses identifying two markers on chromosome 1 that indicate linkage between alcohol and depression (spectrum) disorders. Few similar studies focus on drug use disorders specifically; however, Yang, Han, Kranzler, Farrer, and Galenter (2011) found evidence for potential co-transmission related to genetic risk-based on a genome wide linkage scan, with resulting for promising candidate genes including SRD5A1, UBE3C, PTPRN2, and VIPR2. Together, these findings indicate the potential for some overlap in the genetic diathesis for internalizing and drug use disorders.

For some individuals, this deficit may emerge in early childhood as dysregulated temperament, followed by increased risk for internalizing symptoms that persist into school entry when children are then also at increased risk for poor social engagement and functioning. In social contexts supportive of drug use, these children may move into adolescence forming positive expectations for the effects of drugs, perhaps notably as a potential way of coping with their prolonged anxiety and depression. Early exposure to drug use as a way to successfully alleviate negative affect in the short-term may create strong coping motives for drug use with associated implications for mood regulation, fueling a cycle of negative affect–drug use associations likely to escalate into addictive behaviors. Core to this model, the internalizing pathway suggests that

precursors and putative risk factors for later substance use may arise early in the life course, perhaps as early as the preschool years.

Indeed, early childhood (between the ages of 2 and school entry) is a potentially critical entry point for this risk pathway for several reasons. First, the development of emotion regulation is a focal task of early childhood emerging around age 2 and showing rapid development in the preschool years (Blair & Diamond, 2008). Second, compared with their peers, children with known risk factors for later SUDs (i.e., children of alcoholic and drug using parents) show deficits in emotion regulation that emerge in this age period. For example, Eiden, Lewis, Croff, and Young (2002) found that children of alcoholic parents exhibit less adaptive and less effective emotion regulation strategies compared with children of nonsubstance abusing parents. Finally, early risk markers for substance use disorders may first become evident in this age period. Although rigorous analyses testing the prospective prediction of various forms of substance use from early indicators of emotion regulation and internalizing symptoms are few, existing studies indicate that this association may prove to be complex. For example, Ensminger, Juon and Fothergill (2002) showed that first grade boys classified as shy and aggressive had higher rates of marijuana and cocaine use in adulthood (age 32) than did their peers, though shyness alone did not predict these risk outcomes, and for women being a shy first grader reduced risk for marijuana use in adulthood. Shedler and Block (1990) also showed that adolescents (age 18) classified as frequent users on a substance use index had more symptoms of emotional distress in childhood (ages 7 and 11) than did adolescents classified as experimenters, although adolescent abstainers also showed higher rates of inhibition, shyness, and anxious traits than did experimenters. However, others do not replicate the finding of greater negative affect in abstainers than in experimenters (Tucker, Ellickson, Collins, & Klein, 2006) and some find no association predicting subsequent cannabis use specifically (Oshri et al., 2011). These findings indicate that inhibition and internalizing symptoms may play a role in early risk for later drug use, but the nature of this role, particularly relative to externalizing symptoms, remains unclear.

Thus, although early childhood is not the only developmental period in which risk for the internalizing pathway may emerge, this may be an important time for examining whether potential deficits in emotion regulation are forming as core to risk for the internalizing pathway.

Missing from previous descriptions of the internalizing pathway is a consideration of the mechanisms by which early internalizing symptoms and indices of emotion dysregulation are associated with risk for later substance use and disorder. Two potential factors, however, are the cascading effect of early childhood stress exposure and caregiving environments (see Hussong, Shadur, Reimuller, & Solis, in press). Because we view these mechanisms as working interactively, our treatment of them as distinct in the sections that follow is somewhat false. However, the parsing of risk processes into these two dominant mechanisms has clinical value, particularly in that psychoeducational and psychological interventions currently available or in development may be matched to each.

Early Childhood Stress Exposure

Two interrelated mechanisms that may mediate the relation between early childhood stress exposure and dysregulated stress reactivity, impacting subsequent risk for psychiatric disorder and drug use include alterations in neurobiological reactions to stress (particularly dysregulation of the HPA axis resulting from trauma exposure) and perceptions of decreased emotional security following violence exposure. Although early trauma, maltreatment, and severe stress exposure do not uniformly lead to functional impairment (Cicchetti, 2004), the connection between such early life stressors and subsequent substance use is generally supported (Butt, Chou, & Browne, 2011).

One factor that may, in part, explain risk for the internalizing pathway associated with early stress exposure among vulnerable children is an altered neurobiological stress response (Gunnar & Quevedo, 2007). Because the development of the neurobiological stress response related to early childhood adversity such as maltreatment is reflected in a large, complex literature (Cicchetti & Valentino, 2006), we offer here only highlights that inform risk for an internalizing pathway to substance use and disorder. Accumulating evidence regarding the negative cascading effects of early stress exposure indicate that negative life stressors in young children can lead to dysregulation of the HPA axis, which in turn heighten subsequent stress reactivity to future life stressors, and thereby create a predisposition to psychiatric disorder later in life (McCrory, De Brito, & Viding, 2010). This negative escalating cycle between neurobiological stress responsivity and environmental insult thus appears to continue past early childhood and into the adolescent years (Gunnar & Quevedo, 2007).

More specifically, studies of maltreatment indicate that early experiences of abuse and neglect predict later

neurobiological dysregulation across many systems (i.e., event-related potential responses to emotion stimuli, acoustic startle and neuroendocrine regulation; Cicchetti, 2004), including HPA dysregulation. However, whether reported dysregulation reflects a hypo- or hyperactive stress response varies across studies. As noted by Tarullo and Gunnar (2006), perhaps the most consistent findings are that maltreated children with internalizing problems have elevated morning basal cortisol whereas adults who were maltreated as children (regardless of internalizing problems) often show low basal cortisol and elevated ACTH responses to psychological stressors. DeBellis (2001, 2002 for reviews) posits that cortisol levels that have been elevated for an extended period of time following trauma may result in downregulation of the HPA axis and, in turn, low cortisol levels. These stress responses reflect adaptation over time to a chronic stress or traumatic environment. Consistent with this theory, other studies of maltreatment and the HPA axis find that participants exposed to stress have a blunted HPA response (e.g., Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012; MacMillan et al., 2009). Although some have suggested a blunted HPA response is due to comorbid psychiatric conditions that are associated with trauma exposure, a recent study by Lovallo and colleagues (2012) found that a greater number of traumatic stressors predicted a blunted HPA response in participants with no psychiatric diagnoses. This body of work suggests that despite notable consensus regarding the dysregulating impact on the neurobiological stress response of trauma and chronic stress exposure, such as that reflected in childhood maltreatment experiences, there is less consensus regarding how changes in the HPA axis emerge and change over time to mediate the relation between stress and later adjustment problems (McCrory et al., 2010). Although further study of this developmental process is needed to connect this risk pathway with the negative outcome of later affect-driven substance use specifically, some evidence suggests that compulsive drug use increases with a highly reactive HPA axis (see Andersen & Teicher, 2009) and that those populations at high-risk for substance involvement (namely, children of alcoholic and drug abusing parents) show some evidence of hypoactivity in LHPA response for older youth and adults, but these results remain inconsistent (Dai, Thavundayil, & Gianoulakis, 2002; Dai, Thavundayil, Santella, & Gianoulakis, 2007; Moss, Vanyukov, & Martin, 1995). Moreover, the direction of these effects varies across studies and little information is available on how HPA functioning is associated with drug taking in human studies, particularly in adolescents.

A second potential mechanism linking early stress exposure and later risk for affect-motivated drug use is described in the emotional security hypothesis (offered by Davies & Cummings, 1994). Emotional insecurity is characterized by disruptions in children's feelings (e.g., anxiety, hypervigilance, sadness), behaviors (e.g., inappropriate attempts to regulate family arguments), and cognitions (e.g., skewed views of dangers within relationships; see Cummings & Davies, 2002; El-Sheikh, 2005, for reviews) associated with a basic sense of individual and familial safety that become disrupted following exposure to family conflict and violence. Again reflecting a cascading risk mechanism, prolonged and repeated exposure to marital conflict appears to effectively sensitize or increase children's behavioral and emotional reactivity to conflict (Cummings & Davies, 2002). Over the long-term, children exposed to higher levels of conflict between their parents are also more likely to evidence a relatively wide range of adjustment difficulties, including behavioral, emotional, cognitive, and sleep problems (Davies, Forman, Rasi, & Stevens, 2002; El-Sheikh, Harger, & Whitson, 2001). Moreover, chaotic home environments characterized by family stress and conflict have been found to directly impact children's emotion regulation abilities (El-Sheikh & Cummings, 1997).

Providing a bridge between the emotional security hypothesis and the altered neurobiological stress response theory regarding the effects of early stress exposure, the impact of family stress and conflict impacting children's sense of emotional security appears to have physiological correlates. To date, stress responses including vagal tone, electrodermal responding, cortisol levels, and actigraphic measures of sleep have all been shown to be compromised in children exposed to high levels of marital conflict (El-Sheikh, 2005; El-Sheikh, Keller, & Erath, 2007; Pendry & Adam, 2007). DeBellis (2002) extended this link between environmental stress exposure, physiological stress responding, and problem behavior in development. He underscores that dysregulation in the major biological stress response systems associated with childhood maltreatment, trauma and conflict exposure have adverse influences on brain development that enhance vulnerability to later psychopathology, including posttraumatic stress disorder and depression that precede alcohol and substance use disorders.

Consistent with this perspective, work by Andersen and Teicher (Andersen & Teicher, 2004, 2009; Teicher et al., 2003) suggest that the effects of early stress exposure on the neuroendocrine system (i.e., HPA functioning), brain structure (i.e., smaller mid-portions of the corpus callosum

and attenuated development of the left neurocortex, hippocampus and amygdala; Andersen & Teicher, 2004), and brain function (e.g., electrical irritability in limbic structures and decreased functional ability in the cerebellar vermis), creates susceptibility to compulsive drug use (Andersen & Teicher, 2009) as well as to depression (Anderson, Teicher, Polcari, & Renshaw, 2002). These susceptibilities may only manifest as relevant brain regions and circuits mature with ontogeny. However, with maturation, this early exposure may serve to increase risk for drug use by increasing individual reactivity to drugs of abuse (as supported by animal models) or to reinstate drug-seeking behavior (as found in studies of cocaine and heroin; Andersen & Teicher, 2009).

In sum, early childhood adversity and stress exposure are linked with later risk for substance use and disorder (Butt et al., 2011), are more common among those at-risk for later substance involvement (namely, children of alcoholic parents; Hussong, Bauer, et al., 2008; Hussong et al., in press), and have implications for poorer emotion regulation both early in childhood and later in development (Cicchetti & Valentino, 2006; Gunnar & Quevedo, 2007). Two of these stressors likely include child maltreatment and family violence and conflict. Early childhood stress exposure has implications for the development of neurobiological systems associated with future responses to stress, for changes in brain structure and function, and for the development of emotional security in children, all of which impact emotion regulation and later symptomatology (for an integrative review, see Cicchetti & Valentino, 2006). These same mechanisms may then be partly responsible for early risk associated with an internalizing pathway to drug use and disorder.

The Caregiving Environment

Effective emotion regulation in children depends in part on a biological predisposition to functional regulatory capabilities, but also on the extent to which the environment supports the development of adaptive regulation skills (Thompson, Lewis, & Calkins, 2008). In early childhood, the caregiving environment plays a fundamental role in supporting the development of emotion regulation (Calkins & Hill, 2007). Although there are many ways to characterize the nature of the early caregiving environment (Cox & Paley, 2003), we highlight two aspects of this environment that are posited to be particularly important for nurturing adaptive emotion regulation. These include parenting behaviors that promote a healthy parent–child attachment system more broadly (such asresponsivity or sensitivity) as well as parenting that is specific to the socialization of emotion in children (i.e., parent emotion socialization). Although the two sets of parenting behaviors are related, the former refers to a more general style of parent–child interaction whereas the latter is focused on how parents interact with their children specifically around the issue of emotion.

Both responsive parenting styles and the specific ways parents socialize their children about emotion may be relevant for understanding the internalizing pathway to SUDs and in particular the development of poor emotion regulation during early childhood among at-risk youth, namely children of alcoholic parents. Supporting this hypothesis are several lines of research showing that (1) failure to develop secure attachments accounts for part of the association between insensitive parenting in early childhood and poor emotion regulation, (2) styles of parent emotion socialization that dismiss emotion rather than coach children in how to handle their emotions also predict poor emotion regulation, and (3) parent alcoholism is associated with both insecure attachments and insensitive parenting in early childhood. Also relevant is initial evidence showing that (4) parents with drug use disorders show detriments in parent emotion socialization and that (5) problematic parent emotion socialization is associated with greater risk for negative affect-cued substance use in adolescence.

Attachment theory posits that infants obtain an understanding of the world and what to expect from their relationships with others based on whether their caregivers are consistent, sensitive, and responsive to their needs (Ainsworth, 1979). Attachment styles reflect the nature of the parent–child relationship and are considered to be secure (i.e., children seek comfort from caregivers and respond positively when reunited with caregivers after a separation) or insecure (i.e., children may show no distress when caregivers leave and may show ambivalence or indifference when reunited with caregivers) and these patterns of behavior are evident in early childhood. Secure attachments are associated with a variety of positive outcomes for children, including the healthy development of emotion regulation (Morris, Silk, Steinberg, Myers, & Ronbinson, 2007; Thompson, 2008). Thus, parenting that is sensitive and responsive to children's needs is linked to secure parent–child relationships that in turn predict adaptive emotion regulation (Calkins & Leerkes, 2011). Alternatively, caregiving environments that are not characterized by appropriate titrations of sensitivity and responsivity have been associated with insecure attachment and decreased emotion regulation abilities

in offspring. Some of the negative parenting behaviors demonstrated by caregivers who develop insecure caregiver–child relationships have also been documented in families of children with internalizing symptoms; similarities include high levels of negativity (i.e., criticism, hostility, harshness), detachment and withdrawal (i.e., lack of responsiveness or involvement), control and conflict as well as low levels of consistency or predictability and warmth (Chorpita & Barlow, 1998; Garber & Horowitz, 2002; Ostrander & Herman, 2006). These negative parenting behaviors thus collectively increase risk for children's insecure attachment and poor emotion regulation in early childhood as well as internalizing symptoms as children mature, though these behaviors are not necessarily specific to the context of emotions within the parent–child interaction.

A more specific parenting behavior that is likely to impact children's emotion regulation is parent emotion socialization. Parent emotion socialization broadly includes the ways parents explicitly and implicitly teach their children about if, when, and how it is appropriate to feel and express emotions, and how to manage or cope with emotions (Eisenberg, Cumberland, & Spinrad, 1998). Parents socialize their children around emotions in several key ways, including their reactions to their children's emotions, their own modeling of emotion and regulation, awareness and acceptance of emotions, and direct teaching about children's emotional expression (Eisenberg, Cumberland, & Spinrad, 1998; Gottman, Katz, & Hooven, 1997). Emotion-coaching parents are aware of and accepting of children's emotions and respond supportively to children's expression of emotion through validation, teaching, and problem-solving whereas emotion-dismissing parents may minimize children's emotions and avoid teaching or problem solving around children's emotional experiences (Gottman et al., 1997). Parents' use of emotion-dismissing styles is associated with externalizing and internalizing symptoms (Lunkenheimer, Shields, & Cortina, 2007) whereas emotion-coaching styles are associated with more positive outcomes physically, socially, and academically (Gottman et al., 1997). Parent emotion socialization practices may impact children's emotion regulation skills via their influence on children's regulatory functioning at a physiological level (Gottman, Katz, & Hooven, 1996). For example, children whose parents engage in emotion-coaching strategies have higher vagal tone (i.e., an indicator of more effective regulation; Gottman, 2001).

These parenting behaviors could be particularly important for children of alcoholic parents who may receive less support for developing healthy emotion regulation strategies than do their peers. For example, alcoholic parents may engage in fewer behaviors that foster secure attachments in their children (Seifer et al., 2004). Previous studies show that parents who abuse substances are generally less engaged, less responsive, and exhibit less warmth, sensitivity, and encouragement while interacting with their children (Eiden, Edwards, & Leonard, 2002; Mayes & Bornstein, 1995; Solis, Shadur, Burns, & Hussong, 2012) which compromises the extent to which they can support their children's regulation of emotion (Beeghly & Tronick, 1994). Ingesting drugs of abuse can impair parents' functioning, including a compromised ability to attend to social cues, misattribution of children's behaviors (e.g., attributing negative intent), increased emotional arousal (Kerwin, 2005), and impaired memory and inhibition (Mayes & Bornstein, 1995), all of which may contribute to compromised parenting behaviors. Current parental substance use disorders directly predict lower levels of parental warmth and sensitivity (Eiden, Edwards, & Leonard, 2007; 2004). These insensitive parenting styles are evident even in interactions with infants. For example, compared with nonalcoholic fathers, alcoholic fathers' interactions with their infants are characterized by lower paternal sensitivity, responsiveness, positive affect and verbalizations as well as higher negative affect and aggravation (Eiden, Chavez, & Leonard, 1999; Eiden & Leonard, 2000).

Clearly, parenting behaviors that lack supportiveness and sensitivity can compromise emotion regulation in children of alcoholic parents (e.g., Beeghly & Tronick, 1994). Importantly, such parenting behaviors have been shown to mediate the relations between parental alcohol problems and children's emotion regulation and attachment (Eiden et al., 2004, 2007; Seifer et al., 2004). In a longitudinal study, fathers' and mothers' sensitivity and warmth when their children were 2 years old was shown to mediate relations between fathers' alcohol use disorders when children were aged 12–18 months and children's self-regulation at age 3 years (Eiden et al., 2004, 2007). These findings emphasize the important role of the caregiving environment in linking parental alcohol use disorders and children's emotion regulation over time.

There are currently no published empirical tests of the relation between parent emotion socialization and children's emotion regulation in substance abusing families. However, there is empirical work indicating that parent emotion socialization is an important predictor of children's emotion regulation in other at-risk samples, including low-income families (Brophy-Herb, Stansbury, Bocknek, & Horodynski, 2012), maltreated children

(Shipman et al., 2007), and families impacted by maternal depression (Silk et al., 2011). Moreover, mothers who report physically abusing their children provide greater invalidating responses and fewer emotion-coaching behaviors in response to children's negative emotions compared with nonmaltreating mothers (Shipman et al., 2007; Shipman, Schneider, & Sims, 2005). Additionally, Garber and colleagues (Garber, Braafladt, & Zeman, 1991) demonstrated that depressed mothers responded to children's negative emotion with less supportive and problem-solving behaviors than nondepressed caregivers. Furthermore, mothers with a history of childhood-onset depression were more likely to respond to their young children's sadness, anger, and fear with neglect or punishment (behaviors that could be characterized as emotion dismissing) than mothers without such a history (Silk et al., 2011).

Parental substance use can impact the emotional climate of the home, and children may find that emotional support provided by their parents is often erratic during periods of substance use (Stanley, Cleaver, & Hart, 2010). For example, mothers participating in a qualitative study reported that when they were using (specifically methamphetamine) they exhibited more extreme negative emotions with their children and would generally ignore or would not tolerate their children's emotional expressions (Brown & Hohman, 2006). These factors may contribute to children feeling unsupported in the face of stress or being unable to predict parental reactions and expectations. Collectively, this work suggests that parent psychopathology is related to parent emotion socialization and in turn to children's own emotion regulation.

Critical to the internalizing pathway, parent emotion socialization practices have also been shown to predict adolescent substance use that is associated with negative affect. In contrast to findings regarding symptomatology in younger children, Hersh and Hussong (2009) used an experience sampling approach to show that the likelihood of adolescents using substances was more strongly associated with negative mood in families characterized both by high levels of emotion-coaching and emotion-dismissing styles of parent emotion socialization, perhaps reflecting an overinvolved and critical interaction style. Although these findings are not based on a high-risk sample of children of alcoholic parents, these results suggest that parent emotion socialization practices can impact youth behaviors that are consistent with risk for progressing along the internalizing pathway.

In sum, early evidence of compromised emotion regulation is associated with caregiving environments characterized by insecure attachments, insensitive parenting, and more dismissive forms of parent emotion socialization. In adolescence, these forms of caregiving are also associated with either directly with drug use (Dodge et al., 2009; Wang, Dishion, Stormshak, & Willett, 2011) or as a moderating influence on the daily association between affect and substance use (Hersh & Hussong, 2009). Although no prospective studies directly link early caregiving environments with later affect-motivated substance use, children of alcoholic parents who are at greater risk for later substance use disorders and greater deficits in emotion regulation also are more likely to show comprised early caregiving environments involving this same pattern of deficits.

Finally, although the empirical literature described here relates family climate, parent–child attachment, sensitive and responsive parenting, and parent emotion socialization to children's emotion regulation abilities, internalizing outcomes, and substance use, these findings should not be taken as support for simple uni-directional models of parent and family environment influences on substance use outcomes. Rather, as described earlier for the externalizing pathway, there are reciprocal effects in which children both evoke particular caregiving environments and are influenced by them. Moreover, gene–environment interactions have been proposed that involve genes relevant to the HPA axis (e.g., corticotropin-releasing hormone system genes such as CRHR1), stress response (e.g., MAOA), and the sedating properties of substances (e.g., GABRA2). As described earlier, candidate gene studies suffer from failures to replicate, but there is some evidence that these genes interact with stressors including recent negative life events or early child abuse and sexual abuse to influence substance use in adolescence and adulthood (see Enoch, 2012; Wermter et al., 2010; Young-Wolff, Enoch, & Prescott, 2011).

SPECIFICITY IN THE AFFECT–DRUG ASSOCIATION

One approach to clarifying how the current data fit with the existing negative affect models of drug use is to consider specificity in both the form of affect and type of drug used. Such specificity hypotheses may be guided by theories that posit differential associations in negative affect–drug use associations as a function of both negative affect and drug use. For example, Colder et al. (2010) provided two ways of conceptualizing the relation between affective risk processes and substance use given heterogeneity in

substance use behaviors. First, negative affect may be more strongly associated with substance use that reflects more problematic or severe forms of use. Although inconsistent, findings from studies of the predictors of drug use stages often find that early stages of use (i.e., initiation and experimentation) are unrelated or only weakly related to negative affect whereas later stages of use are more strongly associated with affective predictors. Second, the relation between negative affect and substance use may depend on the class of drugs used, particularly the extent to which the drug is reinforcing or effective when used to alleviate negative affect.

Examining specificity in the association between mood/anxiety and drug disorders, Conway et al. (2006) analyzed NESARC data to examine unique patterns of association among eight specific drug disorders and nine anxiety and mood disorders. Their clearest finding was that the magnitude of mood/anxiety-drug disorder associations was inversely related to the overall prevalence of the specific drug use disorder ($r = -.67$), with the strongest associations emerging for the association between mania and opioid, hallucinogen and cocaine dependence as well as for the association between panic disorder with agoraphobia and tranquilizer, opioid and marijuana dependence.

Testing the drug specificity prediction for substance use behavior while controlling for co-occurring externalizing symptoms, our own work also shows differential prediction of drug use indicators by internalizing symptoms in adolescence. Using an integrative data analysis involving the simultaneous study of three longitudinal, community-based samples of children of alcoholic parents and matched controls (Curran & Hussong, 2009), we examined the unique and interactive effects of internalizing and externalizing symptoms in predicting alcohol use, heavy alcohol use, marijuana use, and other drug use between the ages of 11 and 22 (Hussong, Bauer, et al., 2008; Hussong, Flora, Curran, Chassin, & Zucker, 2008). Results replicate previous studies showing strong and consistent unique effects of externalizing symptoms, predicting both who is likely to use substances (i.e., between-person effects for all four substance use outcomes) as well as when youth are likely to use substances (i.e., within-person effects showing greater use of all four substances in years when youth show elevated externalizing symptoms). Internalizing symptoms also uniquely predicted both who used substances and when substance use occurred, but only for the use of drugs and not for alcohol or marijuana use. Thus, internalizing symptoms were a unique predictor only of more severe forms of substance use, after controlling for externalizing symptoms.

Existing studies also suggest that the unique effects of negative affect on drug use may be affect specific (Colder et al., 2010, Kassel et al., 2010). For example, Pardini, White, and Stouthamer-Loeber (2007) found that adolescent boys had a greater risk for later alcohol-related consequences if they reported higher rates of depressive symptoms; however, these boys had a lower risk for later alcohol-related consequences if they reported higher rates of anxiety/withdrawal symptoms. Other studies also report a protective effect of anxious/withdrawal symptoms on risk for substance use in adolescents (Kaplow, Curran, Angold, & Costello, 2001; Mâsse & Tremblay, 1997) whereas unique effects of an overall index of internalizing symptoms on substance use are more frequently nonsignificant or weak (Brook, Zhang, & Brook, 2011; Fite, Colder, & O'Connor, 2006; Hussong, Curran, & Chassin, 1998). In contrast, effects associated with depression tend to be risk promoting across studies, even after controlling for co-occurring externalizing symptoms (Ingoldsby et al., 2006; Marmorstein & Iacono, 2001; Pardini et al., 2007). Focusing on adults, NESARC findings from Conway et al. (2006) also found support for specificity with stronger associations between mood/depression and drug disorders than between anxiety and drug disorders. Panic disorder with agoraphobia was more strongly related to drug use disorders than was panic disorder without agoraphobia, social phobia, specific phobia, and generalized anxiety disorder. Among mood disorders, major depressive, dysthymia, and mania were more strongly associated with drug use disorder than was hypomania.

One explanation for this distinction is that anxious youth are more harm avoidant, and may be more likely to avoid engaging in illegal or delinquent activities as well as the peer contexts in which such behaviors are often encouraged. On the other hand, depression symptoms are less likely to be associated with harm avoidance and may reflect feelings of distress which underlie coping motives related to substance use or a lack of positive affect, consistent with a sense of anhedonia that may motivate use (Colder & Chassin, 1993). Depression symptoms are also often associated with interpersonal difficulties, which may decrease adolescents' acceptance by mainstream peers and thereby increase the likelihood of affiliating with deviant peer groups which provide access, encouragement and reinforcement for substance use (vis-à-vis the self-derogation hypothesis; Kaplan, 1980). Moreover, growing evidence suggests that alcohol use and depressive mood may share a common genetic diathesis (Kendler, Heath, Neale, Kessler, & Eaves, 1993; Kendler et al., 2003), a finding less evident for anxiety-based disorders.

IMPLICATIONS OF THE EXTERNALIZING AND INTERNALIZING PATHWAYS FOR TREATMENT AND PREVENTION

Consistent with the dominant perspective in Prevention Science (Ialongo et al., 2006), the study of early emerging risk pathways is critical to guide interventions for young children so as to reduce the need for later treatment of more entrenched problem behaviors in adolescence and beyond. Such developmental pathways inform important targets for prevention including when intervention should occur, who should receive the intervention, and what factors should be altered by the intervention. In the case of the externalizing and internalizing pathways, one implication for prevention is the need to target risk mechanisms associated with problems in the development of behavioral and emotion regulation beginning in early childhood for those most likely to experience risk associated with the externalizing and internalizing pathway, namely those with early stress exposure, maltreatment, and impoverished caretaking environments.

As noted earlier, stress exposure early in development has implications for the development of the neurobiological stress response (particularly HPA reactivity) as well implications for changes in brain structure and function that may emerge over development. These early stress experiences are also linked directly with challenges to emotion regulation and also with the development of behavioral control. Unfortunately environments in which such stress exposure are likely to occur are also likely to be those in which impoverished caretaking is available, providing poor supports for children's early development of emotion regulation and behavioral control. Much remains to be learned about how parent substance use disorder may impact these mechanisms, including the relative roles of prenatal and postnatal exposure to alcohol. Protective mechanisms that promote notable resilience observed among this at-risk population also deserve greater consideration. Understanding these risk and protective mechanisms has much to add to the development of effective prevention and intervention programs. In general, the externalizing and internalizing pathways suggest the importance of early, family-based interventions.

Drug Use Effects Pathways: The Nature of Drug Effects

It is virtually axiomatic that exposure to psychoactive substances is a necessary though not sufficient condition for the development of SUDs. Consequently, understanding the effects of substances on the organism is fundamental to developing models of the development and maintenance of SUDs. When conceptualizing the nature of these effects it is important to consider the following points. First, drugs affect the individual acutely; that is, there are time-limited effects of the drug on the organism and, presumably, it is for these acute effects (e.g., for positive or negative reinforcement) that drugs are ingested. These acute effects can have complex time courses in which the early acute effects of the drug may differ from later acute effects of the drug. Early versus later acute effects of drugs may vary in type (e.g., positively reinforcing vs. punishing) as well as intensity. Additionally, the rate or intensity of drug effects typically varies as a function of the dose and route of drug administration with routes of administration that lead to rapid changes in brain levels of the drug more likely to produce stronger effects although the specific reasons for this is a matter of some debate (Samaha & Robinson, 2005). Additionally, the general context in which drugs are consumed (e.g., emotional state, social context) can contribute to the specific type of drug effects experienced. For example, the effects of alcohol appear to differ across drinking settings (Sher, Wood, Richardson, & Jackson, 2005) and alcohol appears to enhance reinforcing aspects of social interaction (Sayette et al., 2012). As noted by Steele and Josephs (1990) in their theory of alcohol myopia, the same dose of a drug can lead to either reinforcement (e.g., pleasure or relief) or punishment (e.g., depression, or crying in one's beer) depending upon the context in which the substance is used. However, it seems likely that strong contextual moderation is more likely to characterize drug effects at intermediate doses of a substance that induces some degree of impairment and mild intoxication in contrast to very high doses that induce severe intoxication (Donohue, Curtin, Patrick, & Lang, 2007).

Drug-induced changes that are chronic, by definition, involve repeated use of the drug. So, for example, although the acute effects of certain drugs may be to transiently increase levels of, say, dopamine or serotonin activity in certain brain regions, over time a chronic pattern of use can lead to chronically low levels of these neurotransmitters. These chronic changes associated with a pattern of prior use are thought to be a key mechanism of how *use* leads to dependence. Importantly, these chronic changes associated with repeated drug use include changes in gene expression, which can then produce longer lasting neuronal plasticity. Recent research suggests that epigenetic mechanisms (including DNA methylation and histone modification) may be one process that results in these drug-use-related changes in gene expression (see, e.g., Nielsen, Utrankar,

Reyes, Simons, & Kosten, 2012; Wong, Mill, & Fernandes, 2011, for reviews). In animal data, drugs that have produced epigenetic changes include alcohol, amphetamines, cocaine, nicotine, and opiates (Nielsen et al., 2012; Wong et al., 2011).

It is important to emphasize that not all individuals who obtain a given level of exposure to a drug go on to develop dependence, highlighting the importance of individual differences (or possibly other environmental factors surrounding drug exposures) in determining those whose substance use progresses to more problematic use and those who do not. Moreover, drugs vary considerably in their apparent addictive liability. For example, some drugs such as LSD, cannabis, and Ecstasy are viewed as having relatively low addictive potential while other drugs such as heroin are viewed as being strongly addictive (Nutt, King, Saulsbury, & Blakemore, 2007). Finally, an individual can be initially exposed to substances at any stage of human development, including in utero, adding another layer of developmental complexity.

Acute Effects

Table 19.1 provides a list of various drugs of abuse that highlights the specific brain regions and neurotransmitter systems affected. It is worth noting that a commonality of all drugs of abuse is that acutely all drugs activate mesolimbic dopamine circuits, a region of the brain associated with reinforcement. These circuits are important not only in understanding the site of actions of various psychoactive drugs, but also other reinforcing activities involving consummatory behavior (e.g., eating; Volkow & Wise, 2005) and other forms of reward seeking (e.g., gambling). There is clearly some variation in the specific mechanisms of drugs of abuse since different lesions of the dopamine system have different effects on response to stimulants vs. heroin vs. alcohol, and drugs that are effective at blocking dopamine are not that effective at reducing drug seeking (Koob & LeMoal, 2006). However, the commonalities in the mechanisms of how drugs produce reinforcement underlie most theories of addiction. For those interested in the development of SUDs, the key issues concern the mechanisms of how acute effects of drugs lead to short-term problems or to chronic changes that result in compulsive drug seeking.

TABLE 19.1 Neurobiological Substrates for the Acute Reinforcing Effects of Drugs of Abuse

Drug of abuse	Neurotransmitter systems affected	Neuroanatomical regions of critical effects	Drug receptors
Cocaine and amphetamines	Dopamine Serotonin	Nucleus accumbens Amygdala	Dopamine transporter (antagonist-cocaine; reverse transport-amphetamine)
Opiates	Dopamine Opioid peptides	Ventral tegmental area Nucleus accumbens	μ and δ opioid (agonist)
Cannabis	Dopamine Opioid peptides	Ventral tegmental area	CB_1 (agonist)
Alcohol	Dopamine Opioid peptides Serotonin GABA Glutamate	Ventral tegmental area Nucleus accumbens Amygdala	$GABA_A$ (agonist) and NMDA (antagonist)
Nicotine	Dopamine Opioid peptides Norepinephrine Acetylcholine	Ventral tegmental area Nucleus accumbens Amygdala	nAchR (agonist)

Sources: Adapted, with permission, by G. F. Koob & M. LeMoal, Drug addiction, dysregulation of reward, and allostatis, *Neuropharmacology, 24,* 97–129, 2001; S. E. Hyman, R. C. Malenka, & E. J. Nestler, Neural mechanisms of addiction: The role of reward-related learning and memory, *Annual Review of Neuroscience, 29*, 565–598, 2006; C. Gotti & F. Clementi, Neuronal nicotinic receptors: From structure to pathology, *Progress in Neurobiology, 74,* 363–396, 2004; G. F. Koob & N. D. Volkow, Neurocircuitry of addiction, *Neuropsychopharmacology, 35,* 217–238, 2010.

Why Do People Use Drugs?

Before considering the issue of chronic drug effects that lead to dependence, it is important to consider why people use drugs in the first place. Chronic effects would not occur unless individuals were motivated to consume drugs for sufficiently long enough periods or in large enough amounts to induce chronic adaptations. Although seemingly a straightforward question, there are large individual differences in subjective drug effects and in individuals' stated reasons for using drugs. The two major theories of drug reinforcement are that drugs with addictive potential tend to either lead to positive reinforcement (e.g., as a euphoriant) or negative reinforcement (e.g., as an anxiolytic, antidepressant, or antinociceptive agent). For many if not all drugs that are positively reinforcing (e.g., stimulants, opiates), activation of dopaminergic regions associated with approach is thought to represent a key mechanism (Wise & Bozarth, 1987) with close involvement of endogenous opioid systems. As noted above, most neurobiological theories of drug addiction and drug effects focus on positive reinforcement. However, for drugs that are classically anxiolytic (e.g., benzodiazepines, barbiturates), increased GABA-ergic neurotransmission in the

septo-hippocampal system represents the neuropharmacological substrate (Gray & McNaughton, 2000). Although stimulants may represent a relatively prototypic drug class for positive reinforcement and benzodiazepines a relatively prototypic drug class for negative reinforcement, drugs can have clear effects on both systems (e.g., alcohol), and many drugs have effects on multiple neurotransmitters. For example, one recent review of self-administration studies concluded that while mesolimbic dopamine circuits might provide a virtually complete neuropharmacological account of psychostimulant reinforcement and is an important contributor to reinforcement from nicotine, alcohol, cocaine, and heroin, other nondopaminergic mechanisms are also important with these latter substances (Pierce & Kumaresan, 2006). For example, alcohol has effects on the major neurotransmitter systems of dopamine and GABA as well as norepinephrine, serotonin, glutamate and others which can explain, in part, the myriad effects it has on mood, emotions, and behavior (Sher & Grekin, 2007).

It is not surprising then that major theories of the etiology of substance use disorders tend to focus upon these two major types of reinforcement. Khantzian (1985, Khantzian, Mack, & Schatzberg, 1974) highlighted the role of the use of drugs as a coping device for those experiencing various forms of psychological distress. From this perspective, much of the underlying motivation for drug use comes from desire to relieve underlying painful affect in an attempt at "self-medication" (as described in our earlier discussion of the internalizing pathway). Although the self-medication hypothesis was developed in the context of treating severely affected clinical cases, generally similar hypotheses were generated by experimentalists studying the effects of alcohol and alcohol-seeking in laboratory rodents (Cappell & Herman, 1972; Conger, 1956). Surprisingly, while seeking euphoriant effects from drugs of abuse was presumably assumed to be a major theory of drug seeking, there is less clear discussion of this in the early literature (although various typologies of alcoholics proposed different motivational bases for drinking among different subtypes; Knight, 1937).

Regardless of the specific neuropharmacological effects underlying the use of a given drug, individuals report a range of different motivations for using drugs and these typically, though not invariably, are related to positive and negative reinforcement. Cox and Klinger's (1988) motivational model of alcohol use posited that alcohol (and presumably other drugs) are consumed for their incentive value in the context of a number of other considerations that must be considered by the user. That is, the incentive value of a substance is not merely the pharmacological effect of the drug but also the individual's learning history, both through direct pharmacological experience as well as social learning (e.g., direct observation, media, advertising) and the current incentive structure guiding his or her behavior). Thus, if individuals have few positive incentives in their lives, the incentive for using alcohol as a positive reinforcer is enhanced. Similarly, if negative incentives predominate, then individuals will be motivated to use to escape or avoid these negative incentives. Within this framework, the decision to use or not to use a drug comes down to its utilities to the user and whether the benefits outweigh the costs of using.

Using this type of model, Cooper (1994) developed a framework for assessing drinkers' motivations to drink, a model that was subsequently extended to other types of drugs. Within this model, which jointly considered both positive and negative reinforcement in conjunction with either an interpersonal or internal focus, she identified four, psychometrically distinct factors: (1) coping motives (internal, negative reinforcement); (2) enhancement motives (internal, positive reinforcement); (3) conformity motives (interpersonal, negative reinforcement); and (4) social motives (interpersonal, positive reinforcement). Most of her early work (Cooper, Frone, Russell, & Mudar, 1995) and subsequent work by numerous investigators has shown that different motives (especially enhancement and coping motives) are differentially associated with various person-variables (e.g., positive affect, personality) as well as with substance use and substance use-related consequences. It should be noted, however, that different drug use motives tend to be correlated with each other and many if not most drug users are versatile in their stated reasons for using. Consequently, although there is a tendency to classify users as using for primarily one motive or another (e.g., someone who drinks for enhancement or coping; Kuntsche, Knibbe, Engels, & Gmel, 2010), the empirical basis for this type of claim is suspect, at least in nonclinical samples of drinkers where this typological issue has been studied (Littlefield, Vergés, Rosinski, Steinley, & Sher, 2013). Additionally, although endorsement of all motives is associated with increased use, some motives such as conformity are less important for heavier users than are social, enhancement, and coping motives. Indeed, coping motives may be particularly pathologic as they show a unique effect on drinking problems even after controlling for amount consumed (Kuntsche et al., 2005).

Surveys of substances users' motives have been developed for marijuana (e.g., Lee, Neighbors, Hendershot, & Grossbard, 2009; Newcomb, Chou, Bentler, & Huba, 1988) and tobacco (e.g., Ikard, Green, & Horn, 1969;

Piper et al., 2004). As noted by Cooper, Kuntsche, Levitt, Barber and Wolff (in press), in a comprehensive review of the drug use motivational literature, there are some differences in the motives that users of different drugs report as one might expect based on variability in their subjective effects and addiction liability. Thus, some scales for assessing marijuana use motives contain motives referring to enhancing creativity or to help sleep whereas scales for assessing cigarette smoking motivations contain motives referring to addiction or habit or cognitive enhancement. However, across various scales for these very different pharmacological substances, both positive and negative reinforcement represent core motivational properties.

Although substance use motives are often viewed as relatively static, there appear to be important developmental changes in motives. For example, developmental changes in motives for drinking track developmental changes in alcohol involvement. Such findings suggest that desistance or maturing out of substance use could represent, in part, changes in the motivational structure of substance use and not, solely, role incompatibility occasioned by the assumption of adult roles (Littlefield, Sher, & Wood, 2010; Sher, Gotham, & Watson, 2004). Equally important, it highlights the importance of considering how motivations for substance use can change over stages of substance involvement.

GENETIC INFLUENCES ON SUBSTANCE USE EFFECTS

Two classes of genes warrant mention with respect to pharmacological vulnerability pathways: genes related to alcohol metabolism and genes related to nicotinic receptors. After alcohol is ingested, it is broken down into acetaldehyde, and then into acetate and water. Acetaldehyde is highly toxic but typically is rapidly down and, in most individuals, acetaldehyde levels following alcohol consumption never get very high. Drugs that create aversive reactions to alcohol like Antabuse (disulfiram) work by inhibiting the enzyme, acetaldehyde dehydrogenase (ALDH) that breaks alcohol down into acetate, resulting in a build-up of toxic acetaldehyde due to ALDH inhibition. One of the genes that code for ALDH, called ALDH2, sometimes has a variant (almost exclusively found in individuals of Asian descent) that encodes an inactive form of the enzyme, leading to an intolerance for alcohol (Shen et al., 1997) and reduced or no alcohol consumption. Although most of the genetic work on alcohol metabolizing enzymes has focused on ALDH2, there is also evidence that enzymes that metabolize alcohol into acetaldehyde (i.e., alcohol dehydrogenases; ADH) may also be associated with consumption. Specifically, variants of the ADH enzymes ADH1B and ADH1C are associated with particularly high rates of activity, leading to acetaldehyde build-up (Shen et al., 1997), also leading to some degree of aversive reaction and lower levels of consumption.

Nicotinic receptors, a subtype of acetylcholine receptor, have high affinity for nicotine and are found at the neuromuscular junction (where the nervous system connects with voluntary muscles) and the brain where they interact with acetylcholine, as well as exogenous nicotine and other substances (and modulate the effects of other major neurotransmitters). There are a number of different subunits of nicotine receptors in the brain that combine in different configurations of five subunits and combinations containing two of these subunits, $\alpha 2\beta 4$, represent a common, high-affinity site for binding nicotine (Greenbaum & Lerer, 2009). The anti-smoking drug varenicline, discussed below, is a partial agonist of receptors containing $\alpha 2\beta 4$ subunits. Although some studies have found associations between genes coding for these subunits, the findings have not been consistent (Li et al., 2006). However, variation in other nicotinic receptor subunits, particularly polymorphisms in the $\alpha 5$-$\alpha 3$-$\beta 4$ subunit cluster on chromosome 15, have been more robustly associated with smoking behavior and tobacco dependence (Bierut, 2009, 2010). It should be noted that these same polymorphisms have, in recent years, been associated with other forms of drug dependence including alcohol dependence, cocaine dependence, and opioid dependence suggesting that variation in this system might be conferring greater general liability to drug dependence than originally thought (Stallings et al., in press).

MODELS OF THE DEVELOPMENT OF CHRONIC EFFECTS AND DEPENDENCE

With repeated experience, (1) the effects of a drug tend to change; and (2) the drug taker tends to change. One of the earliest theories of how the organism develops tolerance to a substance is opponent-process theory (Solomon, 1980; Solomon & Corbit, 1974). Specifically, this theory posits that a positive (or negative) hedonic state (or A-state) elicits a countervailing negative (or positive) hedonic state (or B-state) that serves to counteract the initial state as part of a natural homeostatic mechanism. The theory further posits that with repeated evocations, the B-state

strengthens, thereby reducing the reaction to the drug (that is, the opponent B-state reduces the initial A-state). Thus, the organism's natural homeostatic mechanisms lead to reduced responsiveness to the drug with repeated experience, a phenomenon referred to as tolerance. Tolerance is thought to be important with respect to drug seeking in that it leads to higher levels of drug intake and is associated with other symptoms of dependence. Note that developmental processes are likely to be important in the development of tolerance. For example, in rodent models, chronic administration tends to yield different patterns of adaptive changes in adolescent versus adult rats (e.g., Morales, Varlinskaya, & Spear, 2011) although these changes appear to vary across type of effect being considered and various experimental parameters. In humans, it is well established that tolerance is one of the earliest dependence symptom to emerge in adolescent drinkers (e.g., Lee, Rose et al., 2011), emerging at relatively low levels of use in some individuals.

Although opponent-process theory viewed this process of adaptation as driven by internal, nonassociative homeostatic processes, it was soon discovered that these opponent or compensatory responses were related to cues surrounding drug administration. That is, we can think of the cues surrounding drug taking as conditioned stimuli and the actual direct effect of the drug as the unconditioned stimulus. Siegel and his colleagues (Siegel, 1975, 1976: Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000) demonstrated that *conditioned* compensatory responses (i.e., akin to the hypothesized B-states in opponent-process theory) develop over the course of repeated drug administrations in response to associated external stimuli (e.g., beverage taste, hypodermic needle, social setting), or even early proprioceptive effects of the drug itself or emotions (Siegel, 2005). With repeated drug administrations, these associated stimuli become capable of eliciting conditioned compensatory responses that counteract the direct effects of the drug. In this way, tolerance can be highly situational or context dependent. Consequently, use of a drug in novel circumstances (that lack the situational cues that elicit conditioned compensatory responses) can result in an escape from tolerance (and perhaps even overdose). These situational tolerance effects have been noted for multiple psychoactive substances including opiates, alcohol, and caffeine (Siegel et al., 2000). From the perspective of opponent-process theory and Pavlovian drug conditioning theory, withdrawal phenomena can be viewed as opponent processes acting in the absence of drug effects and involving the same underlying brain systems (albeit in the opposite direction). It is for this reason that resumption of drug intake (initiating a new A-state or primary U.S.) counteracts withdrawal. It should be noted that nonpharmacological processes (e.g., visual processing) appear to involve conditioned compensatory responses (Siegel & Allan, 1998) suggesting that conditioning plays a role in a range of homeostatic adjustments and thus this type of theory is likely more general than a theory of drug effects.

Although opponent-process theory and conditioning theories of tolerance explain how tolerance develops and, how cues surrounding drugs can come to elicit reactions of their own over time (e.g., craving or even withdrawal), they do not address how chronic drug taking alters affective functioning and motivation more generally. Koob and colleagues (e.g., Koob & Le Moal, 2001) have extended opponent-process theory (and, by extension, conditioning theories of tolerance) to account for the broader hedonic changes that are often observed over the course of the development of dependence. According to Koob and Le Moal, these adaptive changes take their toll on the organism by altering the homeostatic hedonic set point by a process known as *allostasis*. That is, over time, there is a change in the natural homeostatic set point so that the B-state no longer merely acts as a countervailing force to balance the evoking A-state but, over time, alters the tonic, hedonic baseline of the individual. This type of allostatic derangement is thought to characterize chronic dependence and this deviation from the (original) natural set point to the allostatic set point is believed to represent hedonic cost to the user. That is, chronic adaptive changes to drug taking dynamically reset homeostatic mechanisms lowering the tonic hedonic set point. These allostatic changes are pernicious in that not only are increasingly large doses of a drug needed to attain a desired state (i.e., tolerance), but the underlying hedonic state further deteriorates, providing further motivation for continued substance use, setting up a vicious, downward cascade of negative affect and compensatory relief drug use. Other theorists have similarly emphasized that negative affect is a core feature of dependence that, in transaction with the larger environment, provides a motivational basis for negative reinforcement (Baker et al., 2004).

To varying degrees, all neurobiological theories of how substance use leads to substance dependence posit that addictive drugs hijack brain systems associated with reward. Robinson and Berridge (1993) in their theory of incentive sensitization posit that craving is the result of a hypersensitization of the dopamine system that increases the incentive salience of drugs and drug-associated stimuli. Critically, this incentive salience (wanting) can diverge from the pleasurable effects of drugs (liking) so that craving

can be experienced even in the absence of any expected positive experience. Although cues surrounding natural rewards (e.g., food, sex, thirst) can also take on special incentive valuates, as noted by Hyman, Malenka, and Nestler (2006), addictive drugs tend to be overvalued at the expense of other reinforcers. This, coupled with the fact that they can have a range of harms associated with them, makes them particularly problematic. That is, although the pure reinforcement value of a drug may be important for earlier stages of drug use, other processes can evolve that motivate more internally driven or compulsive drug taking.

Goldstein and Volkow (2002) argued that although most research has concentrated on the role of limbic regions in the development of addictions, there is substantial evidence implicating frontal structures, in particular the orbitofrontal cortex and the anterior cingulate gyrus. This notion is further developed by Everitt and Robbins (2005) who proposed that the transition from initial use to compulsive use is paralleled by transitions in multiple neural systems, specifically, "prefrontal cortical to striatal control of drug seeking and drug taking along with a progression from ventral to more dorsal domains of the striatum" (p. 1481). The notion that there is a transition from impulsive to compulsive use in the development of dependence is important in several ways. First, it highlights that substance use disorders can be graded by severity that is related to progression of underlying addictive processes. Second, it suggests that early-stage problematic use or mild dependence might be strongly associated with other externalizing problems (owing to shared underlying impulsive processes) but the progression to severe dependence might not be as closely tied to general externalizing and more tied to chronic drug effects. That is, different processes may need to be considered when considering risk factors for substance use versus mild substance dependence versus severe substance dependence.

THE YIN AND THE YANG OF DEPENDENCE: DUAL-PROCESS APPROACHES TO UNDERSTANDING ADDICTION

Contemporary comprehensive theories of substance dependence or addiction posit two distinct systems of addiction. Although there are a range of dual process models, at their core they all posit that problematic substance use or addiction is the product of two countervailing influences, excessive approach tendencies to use the drug and restraining tendencies that hold these processes in check (Orford, 2001). For example, Bechara (2005) posited that decision-making is based on two neural systems: an impulsive system based on the role of the amygdala signaling the affective value of immediate outcomes; and a reflective system based on the role of the ventromedial prefrontal cortex signaling the affective value of long-term outcomes. From this perspective, addictive behavior is the result of a dysfunction of the reflective system that makes some individuals vulnerable to an undue influence of immediate reinforcement (i.e., poor self-control) or, perhaps, vulnerable to the overwhelming incentive value of the substance (i.e., an excessive appetite). This theoretical perspective is useful because it provides a framework for studying functional, endophenotypic components of dependence related to approach and restraint tendencies and suggests multiple, novel targets for intervention. Unlike some traditional theories of health-related behaviors (including substance use) that assume that behavior is rational (e.g., the theory or reasoned action or the theory of planned behavior; Ajzen, 1991; Ajzen & Fishbein, 1980; Fishbein & Ajzen, 1975), dual-processes theories assume both rational and irrational processes play a critical role in addictive phenomena. Although not discussed further here, it can be noted that behavioral economic views on addiction (e.g., Heyman, 2009) view the decision-making processes underlying addictive behavior to be largely the same as those governing nonaddictive behavior but with a key difference. The nonaddicted individual makes decision to optimize his well-being by using a relatively global frame of reference in decision making while the addicted individual maintains a local frame of reference for decision making. That is, decisions concerning self-interest are based on a short-time horizon, leading to decisions that are disadvantageous in the long-term.)

As typically construed (e.g., Deutsch & Strack, 2006), dual-process theories of behavior postulate that there are two psychological systems that jointly determine behavior: (1) a rule-based reflective system; and (2) an association-based impulsive system. For the purposes of the current discussion, we will focus on the basic notion that the impulsive system is associated with the incentive value of various substances and the reflective system is associated with self-regulation and executive control; the decision to use or not use a substance involves the interaction between the two systems. Importantly, the impulsive system is thought to be activated automatically, to not use much in the way of attentional resources, and may often be unconscious. In contrast, the reflective system is dependent upon attentional resources, effortful, and largely conscious. As noted by Wiers et al. (in press), these kinds of prototypic distinctions can often be problematic in that

highly practiced reflective behaviors can become automatized and executed with minimal awareness and that impulsive processes can intrude into awareness. Despite these complexities, the general distinction would appear to have considerable heuristic value.

As noted in our earlier discussion of externalizing pathways, impulsive processes are clearly important in all forms of externalizing behavior that are associated with deficits in self-regulatory processes and executive control. However, the impulsive processes that are specifically associated with drug use (as opposed to reward seeking more generally) are thought to represent key, distinctive features of substance dependence and could map onto neuroadaptive processes such as incentive sensitization and allostasis (Berridge & Robinson, 2006). This is not to say that substance use doesn't affect the reflective system; clearly it could, either through neurotoxic effects on prefrontal brain structures subserving executive functions (e.g., Lyvers, 2000) or because the constant burden of attempting to control excessive impulsive processes can, at least temporarily, wear down self-control (Muraven & Baumeister, 2000). However, it can be argued that the impulsive system conceptually converges with what might be considered the "core" of addiction (Sher, Wolf, & Martinez, 2009). That is, if we can assess impulsive processes, we can assess processes that appear to be distinctly and directly associated with the motivational salience of drugs that, in turn, is intimately related to the neurobiological theories of addiction.

BEHAVIORAL ASSESSMENT OF IMPULSIVE PROCESSES: IMPLICIT COGNITION

To date, researchers have employed a number of tasks designed to assess the degree to which cues associated with drugs are capable of engaging impulsive processes. Most of these are considered *implicit* measures as distinct from explicit *measures* (such as the drug use motivation questionnaires referred to earlier). There are a number of different definitions as to what constitutes an implicit measure although, as a group, they tend to have certain characteristics in common, to varying degrees. According to De Houwer (2006), these include (1) the individual being assessed is unaware of what they are being assessed for; (2) the individual does not have conscious access to the cognition that is being assessed; and (3) the individual has limited control over the outcome being assessed. As described by Wiers et al. (in press), implicit cognitive tasks can be broken down into three broad classes: (1) attentional bias for drug-related stimuli; (2) memory associations; and (3) action tendencies.

Attentional Biases

To the extent that drug cues have acquired incentive salience through their association with a chronic pattern of drug use, they should be able to grab and hold attention and this biasing of attention should interfere with performance on tasks that require more nimble deployment of attention. A variety of different implicit measures show such an effect. For example, the well-known Stroop (1935) color naming task has been adapted to study how drug-related words affect the speed at which a subject can name the color it is written in (relative to control words); that is, if there is an attentional bias to drug cues, it should interfere with the ability to name colors quickly. In a recent meta-analysis of extant drug studies (primarily alcohol, 55%; and smoking, 33%), Cox, Fadardi, and Pothos (2006) found that the size of the Stroop effect was related to several variables including manipulations designed to increase drug use motivation (e.g., drug deprivation) and between-group differences in the heaviness of use. In another recent meta-analysis, Field, Munafò, and Franken (2009) examined the association between attentional bias assessed using a wide range of tasks and craving for various substances: (1) the addiction Stroop, the effect of drug cue exposure on performance on a cognitively demanding task (e.g., Sayette & Hufford, 1994); visual probe tasks (e.g., Ehrman et al., 2002); (2) the attentional blink test, which examines the effect of a prior, drug-related or control stimulus on the detection of a second, quickly presented stimulus (e.g., Waters, Heishman, Lerman, & Pickworth, 2007); and (3) late evoked-related potentials to drug-related and control stimuli. Across the 68 studies included in the meta-analysis (which were heterogeneous with respect to target drugs as well as type of attentional bias assessed), the overall correlation between subjective craving and implicit measures of attentional bias was .19. A number of variables moderated the strength of the overall association, which was stronger for illicit substances such as cocaine, heroin, and cannabis than it was for alcohol and nicotine. As discussed later, these findings open up the possibility of novel treatments that attempt to reverse or undo these biases.

Memory Associations

Although various tests of attentional bias seek to characterize the extent to which drug-related stimuli hijack attention, tests of memory associations (broadly defined) seek

to characterize the network of associations to drug-related stimuli and how automatically they are elicited. Perhaps the best-known test of memory associations is the Implicit Association Test (IAT; Greenwald, McGhee, & Schwartz, 1998), which assesses the differential association (based on reaction time) of drug-related stimuli with positive and negative attributes. Other measures include illusory memory paradigms and association tests that involve asking subjects to produce verbal responses to drug or other cues in either free or controlled association paradigms. As noted by Wiers et al. (in press) across a number of studies that use indirect test instructions (e.g., say the first word that comes to mind) word associations are robust predictors of substance use. Indeed, in a recent meta-analysis, Rooke, Hein, and Thorsteinsson (2008) found that word association tests were the most strongly associated implicit measures of various types of substance use, with a mean correlation of .40.

It should be emphasized that both measures of association and attentional bias are very sensitive to design concerns and much of this literature is confusing and conflicting. Existing meta-analyses are useful at synthesizing findings across multiple studies that vary with respect to subject population, task characteristics, and dependent measures. Although these types of measurements clearly show potential for assessing key addiction-related constructs that are difficult to assess by explicit means, the field is continuing to evolve and identify the range of variables that can affect these assessments.

Action Tendencies

A third type of implicit measure involves assessing the tendency to approach or avoid a given stimulus. In general, this research is based upon the theory that approach or avoidance behaviors are automatically activated by appraisals of the valence of a stimulus. In contrast to research on attentional bias and word association, research on the relation between action tendencies and addiction has not as yet received as much attention. Although some paradigms use association tests like the IAT to gauge approach or withdrawal (e.g., attributes such as *approach* words or *avoidance* words are used instead of more valenced words), the most clearly prototypic tasks involve having the subject perform an action that either involves moving an object towards or away from drug-relevant or control stimuli as in the stimulus response compatibility test (De Houwer, Crombez, Baeyens, & Hermans, 2001) or having subjects either pull towards or push away a stimulus (e.g., using a joystick) that varies in its drug relevance (e.g., Wiers, Rinck, Dictus, & Van Den Wildenberg, 2009). As noted by Wiers et al. (in press), to date these methods have been used with success with alcohol, tobacco, and marijuana users and provide another potential novel assessment of the motivational significance of drugs. Additionally, to the extent that approach to drug stimuli is a learned phenomenon, it raises the possibility that treatments can be developed that can help individuals unlearn these acquired tendencies.

TREATMENT IMPLICATIONS OF THE DRUG EFFECTS PATHWAYS

Understanding the pharmacological mechanisms underlying drug reinforcement and addiction provides strong justifications for some current interventions and has critical implications for the development of new ones. Although it may be most natural to think of pharmacological interventions as the most likely types to target these mechanisms, as described below both pharmacological and behavioral treatments can be considered.

Pharmacological Approaches

One type of treatment that is under investigation involves medications that prevent drugs of abuse from entering the brain. For example, one strategy that has been attempted is to develop nicotine vaccines that bind antibodies to nicotine in the blood, preventing it from crossing the blood-brain barrier and acting on nicotinic receptors in the brain. Although randomized controlled trials have yet to show efficacy of this approach (Hartmann-Boyce, Cahill, Hatsukami, Cornuz, & 2012) researchers believe that this type of strategy warrants further investigation (Fahim, Kessler, & Kalnik, 2013). Similar efforts are also being investigated for treating cocaine and methamphetamine dependence (Kosten, Domingo, Orson, & Kinsey, 2013).

Other pharmacological approaches involve simple substitution of one less harmful form of the drug in place of a more harmful form, as illustrated in nicotine replacement therapy (e.g., nicotine gum, lozenges, nasal spray, and patches). That is, many of the most harmful aspects of smoking are attributable to inhaled smoke and not nicotine per se. Randomized trials both of prescribed medication (Silagy, Lancaster, Stead, Mant, & Fowler, 2002) and over-the-counter medication (Hughes, Shiffman, Callas, & Zhang, 2003) point to efficacy of this approach. Treatment of opiate dependence has employed methadone for many years (Farrell et al., 1994) and the goal of such treatment typically is not cessation but harm reduction with major

outcome measures focusing on various harms of heroin use and retention in treatment (Mattick, Breen, Kimber, & Davoli, 2009). Replacement therapies for cocaine are also under development (Rush & Stoops, 2012).

Although substitution or replacement treatments can be used either as a bridge to abstinence or as a long-term, harm reduction strategy, treatments with medications that block the pharmacological actions of abused drugs at the receptor level (antagonists) have also been developed. For example, naltrexone, a blocker of the mu-opioid receptor, in principle, blocks the euphoriant effects of opiates and is sometimes used to help maintain abstinence in the treatment of detoxified alcoholics. Although originally developed for treatment of opiate addicts, its effectiveness for this problem is not impressive (Minozzi et al., 2011), although it has been shown to be an effective medication for treatment of alcohol dependence and other opiate antagonists are also currently under evaluation for alcoholism treatment (Rösner et al., 2010).

Some medications for addiction have properties of both agonist (substitution, replacement) drugs and antagonist (receptor blocker) drugs. Perhaps the best-known example of such drugs is varenicline, a medication for nicotine dependence that is a partial agonist, having both agonistic and antagonistic properties. Consequently, the agonistic properties provide low-level stimulation of the receptors, avoiding withdrawal, while the antagonist properties mute the effects of nicotine, in effect clamping the receptor at an intermediate level of activity. Varenicline has been shown to be an effective treatment for nicotine dependence, even when compared with other drug treatments such as nicotine replacement and bupropion, and other nicotine partial agonists are being developed (Cahill, Stead, & Lancaster, 2012).

The description provided above is meant to be illustrative by showing several different ways that drug reinforcement pathways can be exploited for developing treatments. A number of other treatments—some approved, some experimental—also exist and include drugs that work on multiple neurotransmitter systems and multiple addictive behaviors. For example, the anti-epileptic drug, topiramate, has been used to treatment alcohol dependence, obesity, and binge eating disorder (Johnson et al., 2007; Marazziti, Corsi, Baroni, Consoli, & Catena-Dell'Osso, 2012).

However, fewer drugs have been developed to address the generalized changes that occur with chronic adaptation to drugs as described earlier with respect to Koob and Le Moal's (2001) allostatic perspective and Baker et al.'s (2004) negative affect theory. These changes in the brain are thought to be attributable to overactivation of the HPA-axis. Consequently, drugs that could restore normal function to this system and prevent the negative downward spiral of inducing further allostatic derangement by self-medicating with the drug of abuse would be of great value clinically. For example, drugs that could antagonize corticotropin-releasing factor might be helpful in unstressing the addicted brain (Koob, 2010). Clearly, the more we know about the underlying neurocircuitry of drug reinforcement and dependence, the more we can identify potential targets for novel therapies.

Behavioral Treatments

There are a number of effective behavioral and psychosocial treatments for substance dependence (e.g., Klimas et al., 2013), including cognitive behavioral treatments (McHugh, Hearon, & Otto, 2010), contingency management approaches (Prendergast, Podus, Finney, Greenwell, & Roll, 2006), and 12-step programs (Ferri, Amato, & Davoli, 2006). While virtually all such treatments could be of benefit to individuals with substance dependence, they are not necessarily based upon models of pharmacological vulnerability (although treatments involving reinforcement for nonsubstance activities such as contingency management are based on the premise that drugs are reinforcers). However, to date, several treatments have been developed from the perspective of countering drug effects and novel treatments are being developed from the perspective of dual-process theories.

For example, to the extent that reactions to drug cues are learned (a perspective consistent with Pavlovian conditioned tolerance and incentive sensitization theory), it should be possible to unlearn these reactions through traditional learning techniques. Influenced by the early development of fear reduction techniques based upon extinction procedures, a number of behavior therapists have attempted to extinguish learned reactions to drug cues (e.g., the sight and smell of cigarettes, alcoholic beverages, or drug paraphernalia). Although such approaches are well motivated theoretically, to date they have not been shown to be a highly effective strategy, producing inconsistent results (Martin, LaRowe, & Malcolm, 2010). Current research in this area is seeking to find ways to make extinction-based procedures more effective with pharmacological aids to facilitate extinction. For example, the drug d-cycloserine has been shown to facilitate classical conditioning of fear in laboratory animals and several groups have tried to see if it can enhance outcome of cue-exposure therapies for substance dependence. To date the findings

have been promising in laboratory models of substance use but not with human patients, but this remains an active area of research (Myers & Carlezon, 2012) as does "thinking through" critical determinants of learning. For example, the context of learning is critical (Bouton, 2000, 2002) and important to generalization. Perhaps more important, the notion that extinction and counterconditioning procedures destroy prior learning is most likely incorrect and, extinction, rather than causing "unlearning" most likely lays down alternative learning that competes with what was learned previously (Bouton, 2002).

It should be noted that aversive conditioning approaches that seek to condition punishment cues to drugs of abuse have been used for decades with varying degrees of success. Perhaps the best known of these is emetic conditioning for alcohol dependence, which, although not used much currently, can be effective if conditioning is established (Howard, Elkins, Rimmele, & Smith, 1991). Aversion treatments in smoking (e.g., rapid smoking) have not been found to be an effective treatment approach (Hajek & Stead, 2000).

Novel learning approaches have been inspired by recent research on implicit cognition in addiction. If automatic approach tendencies are learned, it seems reasonable to see if these can retrained into avoidance tendencies. The same basic laboratory paradigms that are used to assess approach and avoidance tendencies in substance users (e.g., pulling or pushing a joystick) can be used to retrain these tendencies by arranging contingencies so that a patient's task is to, without explicit awareness, push drug cues away and pull nondrug cues towards oneself. Such an approach was employed by Wiers, Eberl, Rinck, Becker, and Lindenmeyer (2011), who found this to be an effective, adjunctive strategy in a controlled trial with a 1-year follow-up. (This approach was subsequently replicated in a new sample; Eberl et al., 2013.) Similarly, experimental treatments aimed at retraining attention away from drug cues have been developed (e.g., Schoenmakers, Wiers, Jones, Bruce, & Jansen, 2007: Schoenmakers et al., 2010) and show initial promise. One of the potentially exciting aspects of these new approaches based on implicit cognition is that they hold promise for being used in less motivated participants and they increase the range of treatment options available to those seeking help.

MACRO INFLUENCES

The etiological mechanisms described above focus primarily on the interplay between individual-level characteristics and the immediate social context (primarily familial and peer influences). However, broader social influences, including neighborhoods, mass media, and public policies (school, community, and legal policies) also influence substance use behavior. Here we review evidence concerning these macrolevel influences.

Neighborhoods

Neighborhood characteristics have been thought to influence many aspects of child adjustment (Leventhal & Brooks-Gunn, 2000). Most research in this area distinguishes two broad features of neighborhoods. *Neighborhood structure* encompasses compositional characteristics of the community (e.g., racial composition, median income, crime) whereas *neighborhood social processes* refer to a community's social organization (e.g., social cohesion and social control). Most of the neighborhood research on adolescent substance use has considered indicators of socioeconomic status (SES), a component of neighborhood structure. These studies have yielded mixed and inconclusive findings. As noted earlier for individual-level SES, some studies find that neighborhood affluence is associated with adolescent substance use (Ennett, Flewelling, Lindrooth, & Norton, 1997; Luthar & Cushing, 1999). Other studies have found that poverty is associated with increased risk for adolescent substance use (Hoffmann, 2002; Smart, Adlaf, & Walsh, 1994), or find no association (Allison et al., 1999; Brenner, Bauermeister, & Zimmerman, 2011). A much smaller number of studies have examined neighborhood social processes and findings suggest that residing in a more socially cohesive neighborhood (trust and shared values among residents) is associated with lower risk for adolescent substance use (Mayberry, Espelage, & Koenig, 2009; Winstanley et al., 2008). When neighborhood effects are found they tend to be small. In general, these findings preclude conclusions about the association between neighborhood characteristics and adolescent substance use. There is a clear need for more systematic research to clarify the etiological role of neighborhoods, and consideration of potential moderators, mediators, and to consider the ways that neighborhoods are conceptualized and measured.

Moderators of Neighborhood Effects

Inconsistent findings suggest that youth may be differentially vulnerable to the effects of neighborhood influences on substance use, and that it may be important to consider potential moderators. There are a few examples in

the literature supporting moderation. Trim and Chassin (2008) found that the effect of neighborhood socioeconomic status depended on whether an adolescent was a child of an alcoholic (COA) or not (non-COA). Residing in a higher SES neighborhood was associated with more rapid increases in alcohol use for non-COAs, whereas residing in lower SES neighborhoods predicted more rapid increases for COAs. The authors suggested that higher SES may be associated with less parental supervision and access to substance using peers for non-COAs and that neighborhood disadvantage unmasked vulnerability associated with parental alcoholism. Scheier, Miller, Ifill-Williams, and Botvin (2001) found that perceived neighborhood danger (perhaps reflecting a structural neighborhood characteristic) was associated with adolescent substance use for high, but not low sensation seekers. Sensation seeking, and possibly the broader construct of behavioral undercontrol, may leave youth particularly vulnerable to negative influences of risky neighborhoods. Age is another possible moderator. Older adolescents spend more time outside of the family home, and may be more vulnerable neighborhood influences. There is some evidence suggesting that low neighborhood SES is associated with higher levels of substance use for older compared with younger adolescents (Mennis & Mason, 2012). Taken together these moderational findings suggest that unmeasured or untested moderating variables may account for some of the mixed neighborhood findings. Related to this point is that neighborhood characteristics are embedded in sociocultural, historical, and geographical contexts (Mrug & Windle, 2009), and regional differences in neighborhood characteristics might account for mixed findings. For example, there are regional differences with respect to ethnic heterogeneity within neighborhoods, residential stability, and depth of poverty, all of which may impact social processes and neighborhood dynamics. Such differences may make it difficult to replicate findings across studies that utilize regional samples. This suggests that large nationally representative samples may be best suited for neighborhood research and that it is important to carefully consider the characteristics of regional samples when drawing conclusions across studies.

Mediators of Neighborhood Effects

Neighborhood characteristics may also be distal influences that operate through more proximal influences in mediational pathways (e.g., Murry, Berkel, Gaylord-Harden, Copeland-Linder, & Nation, 2011). Affiliation with deviant peers is one candidate mediator. Residing in high-risk neighborhoods may increase the likelihood of affiliating with deviant peers who provide access to and support for drug and alcohol use. In a longitudinal study, Gibbons et al. (2004) found that residing in a dangerous neighborhood was associated with high levels of peer substance use, which in turn predicted adolescent use. Chuang et al. (2005) found a similar pattern of effects in predicting adolescent cigarette use, but they did not formally test mediation. Parenting is another potential mediator. Disadvantaged neighborhoods characterized by poverty, low social cohesion, and social control may impair family functioning and compromise parenting, which in turn, increases risk for substance use. Although, as noted above, Chuang et al. (2005) did not formally test mediation, they found that residing in a low SES neighborhood was associated with high levels of parental monitoring, which in turn predicted low levels of alcohol and cigarette use. The protective effect of low neighborhood SES on parental monitoring was contrary to other findings in the literature and unexpected, may reflect regional variability referred to previously. The authors suggested that parents in low SES neighborhoods may use more restrictive parenting strategies to counteract a risky neighborhood context. Although not yet tested, other possible mediators include positive attitudes and weak expectancies about potential harmful effects of drug and alcohol use, and accessibility. Pro-substance use attitudes may be transmitted from adults who themselves have lax attitudes or engage in substance use. Close proximity to alcohol and tobacco outlets is associated with increased levels of use, and outlets tend to be concentrated in disadvantaged neighborhood (Hyland et al., 2003; Wieczorek, 2000).

Neighborhood Conceptualizations

Although neighborhood influences are considered important in ecological conceptualizations of child and adolescent development, there is no clear, single definition of what constitutes a neighborhood. Most studies implicitly conceptualize neighborhoods based on ecological units such census-defined block groups, tracts, or zip codes, but it is not clear whether and why these units represent the best way to define neighborhood boundaries. Another method is to take an idiographic approach and allow research participants or residents define their neighborhood themselves. Perhaps as a consequence of this lack of consensus, the assessment of neighborhood characteristics has varied widely. Different conceptualizations of neighborhood boundaries and assessment methods may yield different conclusions about the influence of

neighborhood characteristics on adolescent substance use. Importantly, boundary conceptualizations and assessment approaches utilized in most neighborhood research is not driven by a theoretical notion of what constitutes a neighborhood.

Taking an innovative, theory-based approach, Hipp, Faris, and Boessen (2012) proposed using information on social ties in the community to create neighborhood boundaries. They argued that social ties are inherent in most conceptualizations of neighborhoods, and that it is therefore important to incorporate social tie information into the creation of neighborhood boundaries. Their approach involves creating boundaries based on a combination of physical distance between residents and their social ties. Once boundaries are thus defined, then structural and social process characteristics can be assessed using multiple methods. Preliminary findings suggest that this approach produces geographically contiguous neighborhoods and a reasonable degree of homogeneity of adolescents' perceptions of neighborhood characteristics within neighborhoods. This method is appealing in that it flows from a theoretical notion of what constitutes a neighborhood (a combination of physical proximity and social ties). A disadvantage is that it is data intensive, requiring collection of sociometric data from most residents in the community. Nonetheless, such a conceptually driven method for defining neighborhoods may have utility in clarifying the role of neighborhoods in the etiology of adolescent substance use.

Media

Media influences have been studied both as risk factors for increasing substance use and as a tool for substance use prevention. Substance use is often presented as cool, fun, and relaxing in the media (Stern, 2005), and this combined with the limited regulation of alcohol and tobacco advertising suggests that the media is a potential source of pro-substance use messages. Media portrayals of substance use occur through many sources, including in-store displays, billboards, print, the Internet, television, and movies, and the amount of time adolescents spend with media exceeds the time they spend with friends and family (Rideout, Foehr, & Roberts, 2010).

Advertising

Exposure to alcohol and cigarette advertising is associated with higher rates of adolescent smoking and drinking (Anderson, de Bruijn, Angus, Gordon, & Hastings, 2009; Hanewinkel, Isensee, Sargent, & Morgenstern, 2011). Although there are restrictions on cigarette advertising, youth continue to report exposure to cigarette advertising through in-store displays, magazines, and the Internet (Centers for Disease Control and Prevention, 2005). Cigarette manufacturers have reduced advertisements in magazines with high youth readerships. However, they have shifted the brands advertised; such that brands popular with young people are more likely than brands popular with adults to appear in magazines with high youth readership (King, Siegel, Celebucki, & Connolly, 1998). Similarly, the number of alcohol advertisements that appear in a magazine is positively associated with the percent of young readers (Garfield, Chung, & Rathouz, 2003), and types of alcohol popular with youth are more likely to appear in magazines that young people read (King et al., 2009). Although cigarette advertising has been banned from television since 1971, alcohol advertising is still permitted. Adolescents exposed to more alcohol advertisements on television are at increased risk for drinking (Smith & Foxcroft, 2009) and there has been a recent increase youth exposure largely due to increases in alcohol advertising on cable television (Center for Alcohol Marketing and Youth, 2010).

Entertainment Media

Entertainment media (television, movies, music, and music videos) portrayals of alcohol, cigarette, and other drug use are largely positive, rarely show negative consequences of use, and influence adolescent attitudes about substance use (Strasburger & The Council on Communication and the Media, 2010). According to a content analysis of television programs in the year 2000, most top-rated prime-time shows mentioned or depicted substance use (mostly alcohol use), and 49% included humorous references to substance use (again mostly alcohol use; Christenson, Henricksen, & Roberts, 2000). Exposure to smoking or drinking in movies is related to rates of adolescent smoking initiation (Charlesworth & Glantz, 2005) and adolescent alcohol use (Sargent, Wills, Stoolmiller, Gibson, & Gibbons, 2006). A content analysis of 24 G-rated movies suggested that tobacco and alcohol appeared at least once in 75% of the movies, and nearly all depictions were positive (Ryan & Hoerrner, 2004). Of the top-grossing films between 1999 and 2001 with a teen as a major character, 17.1% showed teens smoking, 40% showed teens drinking, and 15.1% showed teens using other drugs, with few negative consequences of use depicted (Stern, 2005). Smoking in movies is associated with positive characteristics that are

likely appealing to adolescents, including rebelliousness, glamour, and romance, and a national study in 2009 found that many movies rated G, PG, or PG-13 showed or implied tobacco use (39%), with a higher rate in PG-13 movies (54%; Centers for Disease Control and Prevention, 2010b. A recent study found that there was a 7% per movie increase in occurrences of use or implied use of tobacco (13.1% to 14.0%) in top-grossing movies between 2010 and 2011 (Glantz, Iaccopucci, Titus, & Polansky, 2012). Most popular movies depict alcohol. A study of popular movies between 1998 and 2003 showed that 83% of popular movies depicted alcohol use, and 15.2% of G- and PG-rated movies depicted an inebriated character (Cin, Worth, Dalton, & Sargent, 2008). In short, a positive portrayal of substance use in movies is the norm. Exposure to substance use in movies is associated with increased risk for substance use (Koordeman, Anschutz, & Engels, 2012).

Music and music videos represent another source of substance use messaging. Content analysis of popular songs from 2005 suggested that over 30% included references to substance use, most of which were positive (Primack, Dalton, Carroll, Agarwal, & Fine, 2008). This study estimated that the typical adolescent is exposed to 84 references to substance use per day through listening to music. The more music that youth listen to is associated with increased risk for substance use (Primack, Kraemer, Fine, & Dalton, 2009).

Methodological Issues

Although there are clear links between media exposure and adolescent substance use, a potential critique of this research is the question of direction of effects. Rather than media exposure causally influencing the onset and escalation of adolescent substance use, it is possible that adolescent substance use leads to the selection of media and contexts that reinforce substance use behavior and attitudes (Slater, 2007). However, it may be difficult for youth to avoid exposure to pro-substance use messages given the proliferation of substance use in the media. It is also possible that links between media and substance use are attributable to common third variables. For example, behavioral undercontrol may increase an individual's preference for substance use saturated media and may also increase the likelihood of substance use, and when this variable is statistically controlled, the association between media exposure and substance use may no longer be detectable. However, accumulated longitudinal evidence from studies that have statistically controlled for potential confounding variables (e.g., personality, demographics, parenting) have shown that media exposure prospectively predicts adolescent substance use (e.g., Koordeman et al., 2012; The National Cancer Institute, 2008; Slater & Hayes, 2010).

Not all youth appear to be equally susceptible to media exposure. Several studies have examined potential moderators of the effect of media exposure, and findings suggest that behaviorally undercontrolled youth (e.g., high sensation seeking, poor self-regulation) are more vulnerable to the effects of media exposure on adolescent substance use (Stoolmiller, Gerrard, Sargent, Worth, & Gibbons, 2010; Wills et al., 2010). These studies suggest a specific subgroup that can be selected for targeted interventions. Studies have also examined mediational mechanisms, and this body of work suggests that media exposure influences adolescent substance use by increasing affiliation with substance using peers and positive attitudes about substance use (Koordeman et al., 2012; Slater & Henry, 2013). Understanding mechanisms provides additional points of intervention that may help reduce the impact of media exposure.

Although media exposure plays a role in the etiology of adolescent substance use, there are a number of issues that remain unresolved. First, measures of media exposure have focused on simple aggregations of frequency of exposure, but all portrayals of substance use in the media may not have the same impact. Aspects of socioemotional context (e.g., emotional valence and arousal, the degree to which youth identify with the portrayal) may influence the salience of media portrayals of substance use. Second, studies that have examined moderation have focused on vulnerability models (e.g., risk factors that increase vulnerability to mediate influences). However, protective mechanisms are also important and have the potential to inform intervention efforts. Focusing on factors that might buffer the impact media exposure, such as open parent–child communication, affiliation with peers who don't engage in substance use, has the potential to inform target variables for preventive interventions. Finally, media exposure may vary across age and stage of use and very little research has considered this question. Media exposure may be a more powerful influence in early adolescence during the early phases of substance use when social influences may be particularly important, but less of an influence in later stages of problem use. Very little research has examined these questions. Understanding age and stage differences has the potential to inform questions about when and for how long youth should be protected from media exposure.

Media messages have also been used in public health campaigns as an intervention to reduce adolescent substance use. Although most adolescents have seen or heard antidrug messages through a variety of sources (e.g., radio announcements, commercials, pamphlets, and posters), the effectiveness of many of these messages is unclear. However, there are examples of effective public awareness campaigns. *Truth* targeted adolescent attitudes about smoking, and involved a counter-marketing effort that provided adolescents with facts about the harms of smoking and about the tobacco industry's marketing practices. This campaign effectively promoted negative attitudes towards the tobacco industry and smoking, which in turn, predicted decisions about smoking (Cowell, Farrelly, Chou, & Vallone, 2009; Farrelly, Nonnemaker, Davis, & Hussin, 2009). A recent study used Nielsen Media Research ratings to examine the impact of anti-drug television advertising on adolescent drug use (Terry-McElrath, Emery, Szczypka, & Johnston, 2011). Results suggested that exposure to anti-drug advertisements was associated with some positive effects regarding marijuana (e.g., disapproval of use, lower odds of use, and greater perceived risk of use), but these effects varied across middle and high school youth. This suggests that the effectiveness of public awareness messages can differ across subpopulations of youth, and a crucial issue is to understand the kinds of messages that are most effective for different populations. This an important direction for future research because the idea that one type of message works for all youth does not appear to be emerging in the literature.

The National Youth and Anti-Drug Campaign (NYADC) is an informative example with respect to considering targeting public awareness messages for specific populations. The NYADC was funded by the Office of National Drug Control Policy to develop a media campaign to prevent substance use initiation and reduce use among occasional users. Initial results suggested that the campaign was not effective, and may even have had iatrogenic effects (Hornik, Jacobsohn, Piesse, & Kalton, 2008). The campaign was revamped to target marijuana use among a high-risk group, high sensation seekers. The new public service announcements were crafted to be high in sensation value (e.g., messages that elicited strong sensory, emotional, and arousal responses). Such messages have been shown to be appealing to high sensation seekers (Palmgreen et al., 1991). This revamped campaign (the Marijuana Initiative) was found to be successful at reducing marijuana use and weakening positive marijuana beliefs among high sensation seekers (Palmgreen, Lorch, Stephenson, Hoyle, & Donohew, 2007). These findings suggest that public awareness campaigns can be successful when designed to be salient to targeted groups of adolescents.

Schools and Communities

Schools and communities can implement antidrug policies and prevention programs, and provide a context within which problem substance users can be identified and connected with service providers. Antismoking policies in schools are effective at lowering rates of adolescent smoking when they are consistently enforced (Adams, Jason, Pokorny, & Hunt, 2009; Lipperman-Kreda, Paschall, & Grube, 2009). However, policies that ban smoking for students, but allow it for staff are less effective (Trinidad, Gilpin, & Pierce, 2005). Zero-tolerance policies mandate predetermined punishments (e.g., suspension, expulsion) but have not been systematically evaluated, so it is unclear if they are effective. Some schools conduct drug testing (mostly of student athletes) and drug searches, but research on these approaches is limited and inconclusive (e.g., James-Burdumy, Goesling, Deke, Einspruch & Silverberg, 2010; Yamaguchi, O'Malley, & Johnston, 2004).

Other school-based prevention efforts take the form of drug prevention programs. These programs vary widely, and can include curriculum and instruction, recreational programs, and counseling directed at students, as well as organizational and structural changes in scheduling, physical features of the school, and classroom management practices. Reviews of school-based prevention programs suggest that effective prevention programs share some common features (Botvin & Griffin, 2007; Cuijpers, 2002; Gottfredson & Wilson, 2003). These include (1) a focus on aspects of social influence, such as building skills in recognizing and resisting peer pressure; (2) providing accurate information about rates of substance use to correct misperceptions that substance use is normative; (3) increasing motivation not to use; and (4) utilizing interactive methods (e.g., facilitated discussions, small group activities). Although effective school-based prevention programs have been developed, they have not been widely disseminated, and understanding and overcoming the barriers to dissemination remains an important goal.

Community prevention programs typically target multiple aspects of the community including law enforcement, schools, religious institutions, and retailers. The broad focus of these programs is appealing given the broad array of contexts and factors known to influence adolescent substance use. Most of these programs have not been adequately evaluated and so whether they are effective is

an open question. Randomized clinical trials provide the most rigorous test of interventions, but they are difficult to implement when testing community prevention programs. A few community prevention programs have shown some promising results using randomized clinical trials (e.g., Hawkins et al., 2008; Perry et al., 2002). In addition, community-university partnerships implementing multicomponent interventions (including school-based and family-focused interventions) have shown reductions in substance use outcomes (Spoth et al., 2013).

Health Care System

Opportunities for prevention (as well as treatment) also exist within the health care system, within which routine screening and early intervention could be incorporated. Although there have been longstanding recommendations for physicians to screen adolescents for substance abuse and to provide brief interventions, and the tools exist to do so, these recommendations have not been widely implemented (Kokotailo & the Committee on Substance Abuse, 2010; Van Hook et al., 2007). Most health care providers lack the necessary training, and empirically validated treatment approaches have not been widely disseminated (Feinstein, Richter, & Foster, 2012). Indeed, although evidence-based treatments exist (Waldron & Turner, 2008), very few adolescents with drug disorders receive treatment (fewer than one in five in one study; Merikangas et al., 2011). Perhaps related to the lack of treatment services, in the United States, the juvenile justice system is the largest referral source for adolescent drug treatment (Nissen & Pearce, 2011). The Affordable Care Act will bring the possibility of transforming health care provision and substance abuse treatment to a fee-for-service model, making it easier for health care providers to be paid for screening and intervention services (Buck, 2011). The Affordable Care Act may also expand funding for uninsured persons and prevention services.

Taxation, Regulation, and Youth Access Policies

Government policies regarding taxation, regulation, and enforcement can have a strong influence on adolescent substance use by reducing access to drugs and alcohol and transmitting strong antidrug messages. Increasing taxes, and thereby increasing the cost of cigarettes and alcohol, is associated with decreases in adolescent smoking and drinking (Carpenter & Cook, 2008; Laixuthai & Chaloupka, 1993). Smoking bans in the workplace, restaurants, and other public spaces are associated with lower rates of adolescent smoking (McMullen, Brownson, Luke, & Chriqui, 2005). Laws restricting adolescents' access to cigarettes (prohibiting sales to minors or prohibiting minors from possessing cigarettes) generally show weak effects on reducing adolescent smoking, despite reductions in illegal sales (Richardson et al., 2009). This is likely due to adolescents having other means of access to cigarettes (e.g., friends, parents; Fichtenberg, & Glantz, 2002). Increasing the minimum legal drinking age to age 21 in the United States was associated with reductions in adolescent alcohol use and disorder (Carpenter, Kloska, O'Malley, & Johnston, 2007). This effect of raising the minimum drinking age suggests that similarly raising the legal age to purchase cigarettes, which is 18 years old in most states, to 21 might reduce rates of adolescent smoking.

Cigarette, alcohol, and drug manufacturers devote substantial resources to promote their products, and there have been attempts to limit adolescent exposure to these efforts. In 1971 cigarette advertising was banned from radio and television. In 1998, the Master Settlement Agreement prohibited cigarette manufacturers from directly and indirectly targeting underage youth in advertising and promotions, and several manufacturers also agreed to limit advertising to magazines with less than 15% youth readership. In 2003, the alcohol industry agreed to limit advertising in television, magazine, and radio to venues where 70% or more of the audience was 21 years old or older. As noted earlier in our discussion of advertising exposure, these restrictions may be insufficient to impact adolescent smoking or alcohol use. In summary, policymakers can play a significant role in reducing adolescent substance use by using a multipronged approach. Effective policies are likely to include implementing public awareness campaigns, limiting access to tobacco and alcohol products by raising taxes on these products, expanding tobacco bans and raising the minimum age for purchase of tobacco products to 21, limiting youth exposure to tobacco and alcohol advertising, and expanding access to evidence-based prevention and treatment services.

CONCLUSIONS

As this chapter illustrates, studying the developmental psychopathology of substance use and substance use disorders is a complex and multidisciplinary endeavor that involves both broad pathways (not specific to substance use) that underlie behavioral and affective regulation and reactivity as well as consideration of pathways that are specific

to substance use effects. Epidemiological approaches illustrate the importance of societal-cultural contexts in influencing patterns of substance use prevalence. Epidemiological data speak to the need for continuing surveillance, including assessments of newly emerging substances, providing public health messages concerning substance use risk, and monitoring the potential for drug substitution effects. Studies of age-related trajectories of substance use speak to the risk associated with early onset of use, including the potential utility of delaying onset as a means of reducing the prevalence of substance use disorder. However, although substantial empirical work has focused on antecedents of substance use transitions in adolescence and emerging adulthood, there has been less application of a developmental psychopathology perspective to study substance use outcomes in midlife and later life. Age-specific etiological factors in mid-life and late-life (including the effects of role transitions) are in need of future study. Future research on aging samples is warranted, particularly because higher substance use among the baby boomer cohort forecasts increases in alcohol problems among older individuals

Studies of the internalizing and externalizing pathways illustrate the utility of many features of the developmental psychopathology perspective, including support for the principles of equifinality and multifinality, the importance of studying pathways of risk and resilience at multiple levels and the importance of developmental cascades. Studies of the externalizing and internalizing pathway converge with studies of substance use effects in pointing to adolescence as an important period of risk, both in terms of the neurobiology of adolescent brain development creating a period of vulnerability for risk-taking behavior in general and in terms of elevated sensitivity to substance use effects. However, these pathways also clearly demonstrate that the etiology of substance use disorders has roots in early development, and the internalizing and externalizing pathways point to the importance of early adversity, parenting, and family climate as well as pre-natal exposure and gene–environment interplay in the development of capacities for both behavioral and affective self-regulation. The internalizing and externalizing pathways thus support the importance of early family-based interventions as an approach to preventing later substance use and substance use disorder (as well as associated mental health problems). Mediators common to the internalizing and externalizing pathways (including parenting and family environment and affiliation with substance use-promoting peers) support the inter-relations between the two models. Methodological approaches including the use of experience sampling methods in real time, genetically informative designs, and greater specification of the roles of individual facets of behavioral undercontrol and of negative affect are useful future directions. Moreover, given variation in etiological influences with both age and stage of substance use, studies that allow greater specification of age and stage variation are important.

Studies of the etiological pathways related to substance use effects reinforce the importance of considering stages of substance use involvement including the transition from impulsive to compulsive use. These models also point to the possibilities of novel treatment interventions, both pharmacological interventions to counter substance use effects or counter the harms of substance use effects and behavioral interventions to extinguish automatic positive associations and approach responses. One important research agenda for the substance use effects pathways is to better understand the effects of adolescent exposure to substance use, particularly possible neurotoxic effects on cognitive functioning, self-regulation, reward sensitivity, and personality development. These studies should identify the dose–response relation between adolescent substance use and its potential sequelae and should specify the role of particular substances within the context of correlated risk factors (including the use of multiple substances). At the time of this writing (2013) substantial research efforts are underway to achieve this goal through prospective studies.

Studies of macrolevel social influences suggest that public policy can have substantial impact on reducing the population prevalence of substance use including the tax policy, restricting access (including the legal age of use), and raising public awareness. Future research is needed to understand the effects of public policy on various high-risk subgroups within the population and the potential for achieving targeted effects (particularly as applied to media campaigns).

Finally, one of the greatest needs revealed by this large and complex literature is the need to narrow the gap between our growing empirical understanding of the development of substance use disorders and the preventive and treatment interventions that are available to the public. Although evidence based interventions have been developed both for prevention and treatment, they are not routinely implemented or implemented at a large enough scale to have an impact on the public health. Given the significant public health burden of substance use disorders (including mortality, morbidity, and economic cost), emerging innovations in health care delivery systems and funding models should include the provision of evidence-based prevention and treatment interventions for substance use and substance use disorders as an important priority.

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CHAPTER 20

Bipolar Disorder from a Developmental Psychopathology Perspective: Focusing on Phenomenology, Etiology, and Neurobiology

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BIPOLAR DISORDER: CONCEPTUALIZED WITHIN A DEVELOPMENTAL PSYCHOPATHOLOGY FRAMEWORK

Developmental Psychopathology

The purpose of this chapter is to consider how a developmental psychopathology perspective can advance our understanding of the wide spectrum of bipolar disorders (collectively referred to as bipolar disorder throughout the text). Developmental psychopathology promotes an integrative scientific approach that emphasizes the importance of investigating normative and atypical developmental processes. This perspective contends that psychopathology is best understood by considering normative processes from which symptoms may arise (e.g., Cicchetti, 1990; Cicchetti & Toth, 2009; Sroufe & Rutter, 1984). Indeed, bipolar disorder "magnifies common human experiences to larger-than-life proportions" as individuals experience both the devastating lows of depression and the extreme highs of mania (Goodwin & Jamison, 2007, p. xix). Accordingly, it is critical to consider how individuals experience and adapt to derailments from normal development, ideally from a longitudinal perspective. Additionally, recognizing that psychopathology does not exist in a vacuum, the developmental psychopathology approach attempts to discern the process by which extreme variations in emotions and behaviors become maladaptive and disrupt the path of normative development. Developmental psychopathologists are interested in the critical biological and environmental factors that prevent individuals from reaching developmental milestones and those that help protect individuals who are at high-risk for mental illness. This approach assumes a dynamic interplay between salient neu-

robiological, environmental, and psychological systems, necessitating the understanding of transactional processes (Cicchetti & Tucker, 1994). Additionally, it is recognized that developmental liabilities are likely to constrain the ease of adapting to new developmental challenges, resulting in probabilistic tendencies toward maladaptive outcomes. Those at risk for or diagnosed with bipolar disorder in childhood and adolescence typically experience challenges that interfere with an individual's ability to master normative age-salient developmental tasks. Problems often arise in regulating strong emotions, forming meaningful interpersonal relationships, or developing a sense of competency based on mastery experiences. Manic or depressive symptoms can also limit an individual's intra- and interpersonal resources, preventing the individual from navigating critical developmental transitions encountered in childhood and laying the foundation for problems that persist into adolescence and adulthood. Fortunately, while these probabilistic tendencies are critical, they are not deterministic. We now know that development is malleable, meaning that similar developmental liabilities can result in multiple outcomes (Cicchetti, Rogosch, & Toth, 1997). Given these considerations, the developmental psychopathology approach is especially relevant to the study of youth at risk for bipolar disorder and those already exhibiting these disruptions early in development.

Despite the applicability of a developmental psychology perspective to the study of bipolar disorder, research from a developmental perspective has occurred relatively recently. In part, the slow growth of this field may reflect the slow pace of research on adult bipolar disorder during much of the twentieth century. Efforts to comprehensively compile the research on adult bipolar disorder weren't published until 1990 with Goodwin and Jamison's *Manic Depressive Illness: Bipolar Disorders and Recurrent Depression*. Additionally, the field has been slow to study bipolar disorder in youth, particularly in children. It is notable that in the two-volume second edition of Goodwin and Jamison's textbook (2007), the authors included two chapters on children and adolescents: one on the description of bipolar disorder in youth and one on its treatment. Significant advances were also made around this time with the publication of two other academic books describing current knowledge (Geller & DelBello, 2005) and treatment (Geller & DelBello, 2008) of pediatric bipolar disorder.

The focus on bipolar disorder from a developmental psychopathology perspective has been recent as well. Efforts to bring attention to the paucity of longitudinal research or work that used a developmental framework to directly examine risk factors of bipolar disorder (e.g., DelBello & Geller, 2001) continue to be largely relevant today. With a notable exception (Cicchetti & Toth, 1995b), the major developmental psychopathology handbooks have rarely included a discussion of bipolar disorder (e.g., Achenbach; 1982; Cicchetti & Cohen, 2006; Lewis & Miller, 1990; Luthar, Burack, Cicchetti & Weisz, 1997). There are a few major reasons why the developmental psychopathology focus on bipolar disorder has progressed rather slowly. First, developmental discontinuity has historically been emphasized in research on bipolar disorder, as in the *DSM-III*. As one researcher observed, "For decades the field operated as though bipolar disorder sprang fully formed from the brow of young adults" (Youngstrom, 2010, p. 68). Second, in the mid to late twentieth century, evidence from behavioral genetics indicated that the disorder was primarily caused by genetic factors. These findings likely obfuscated the environmental and developmental factors involved in the etiology of the disorder and helped foster the flawed impression that mental illness was deterministic—either something one had or didn't have—rather than a set of symptoms that can change over time, depending on one's environment, personality, and treatment. Relatedly, researchers have only recently acknowledged the importance of incorporating multiple levels of analyses into models of pathophysiology (Cicchetti & Dawson, 2002). Third, a proper developmental study of bipolar disorder demanded developmentally appropriate longitudinal research (including developmentally appropriate measures of mania and depression), which is both expensive and time-consuming. As a result, foundational research on bipolar disorder utilizing a developmental psychopathology framework has only been conducted relatively recently.

With this in mind, it is noteworthy that this is the first developmental psychopathology handbook series in which a chapter is fully dedicated to bipolar disorder. That is not to say that this chapter is the first work to outline the major themes and studies in the field. This chapter attempts to build on and complement seminal texts compiled by Miklowitz and Cicchetti that evaluated bipolar disorder from a developmental perspective and gave increasing prominence to the study of bipolar disorder in children and adolescents. These works, a special issue of *Development and Psychopathology* (Miklowitz & Cicchetti, 2006) and a similar collection of work that appear in the text, *Understanding Bipolar Disorder: A Developmental Psychopathology Perspective* (Miklowitz & Cicchetti, 2010), systematically addressed the (1) phenomenology and diagnosis, (2) onset, prognosis, and course, (3) etiology/risk and protective mechanisms, (4) treatment, and

(5) personal accounts of bipolar disorder. These recent efforts significantly advanced the field by showing that a multidisciplinary developmental approach to the study of bipolar disorder has important scientific and clinical applications, and can better help elucidate both normative development and the progression of the disorder. Some of the key themes discussed in these texts will be discussed, updated, and elaborated on in this chapter.

Chapter Overview

This chapter will use a developmental psychopathology perspective to review foundational and recent research on bipolar disorder, particularly research on risk and protective factors for the illness (Cicchetti, 1990). In the first section we discuss the phenomenology of bipolar disorder. As this is a field in which scientific controversies abound, we begin this section by discussing bipolar disorder in a historical context and the circumstances leading to the current *DSM* diagnosis for pediatric and adult bipolar disorder. We summarize major themes pertaining to clinical diagnostic approaches and emerging empirically derived approaches that focus on symptom manifestations. We also briefly discuss emerging approaches that deemphasize self-report and focus on dimensions of observable behavior and neurobiological indices. We close this section by summarizing the onset and course of the disorder. In the second section of this chapter, we consider etiological theories of the illness. Family aggregation patterns of bipolar disorder have been acknowledged for the past century, but recent advances are beginning to modify our understanding of the disorder's underlying environmental and genetic mechanisms. Here, we will describe the wide range of genetic and environmental etiological theories behind adult and pediatric bipolar disorder, with a special emphasis on the new technologies and scientific advances that are informing this research. Third, because bipolar disorder is considered a neurodevelopmental disorder, we will consider some of the most important neural mechanisms that have been implicated as potential precursors or are evident in youth who are diagnosed with bipolar disorder. Although the majority of neurobiological research has focused on adults diagnosed with bipolar disorder, the focus of this section will be on the advances relevant to developmental neurobiology and psychopathology, much of which have taken place in the past decade. While the neurobiological advances cover a broad range of fields (e.g., neurotransmitters, neurohormones, neuropsychology performance), we will primarily focus on brain imaging research. We conclude the chapter with suggestions for translational research by considering how our current knowledge of these developmental and neurodevelopmental models may inform intervention science and help identify promising new directions for future research.

At the onset of this chapter, a brief overview of the use of relevant terms is needed. Throughout this text, we will focus on bipolar disorder that includes the wider spectrum of bipolar disorders, commonly including bipolar I and II disorders and sometimes cyclothymic disorder and bipolar disorder not otherwise specified (NOS). When specific diagnoses are considered (e.g., bipolar I disorder), they will be specified accordingly. Although there are considerable differences in childhood and adolescent diagnoses of bipolar disorder, "pediatric bipolar disorder" will be used when referring to the disorder among children or adolescents. It is worth noting that pediatric bipolar disorder has no official definition in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994; 2013), but generally refers to individuals younger than age 18 years or those who have not yet transitioned to adulthood.

CLASSIFICATION AND PHENOMENOLOGY: HISTORICAL CONTEXT AND RECENT ADVANCES

Assessment and classification systems are critically important to scientific advances and clinical care because they powerfully shape research on the etiology, course, outcomes, and treatment of emotional and behavioral problems (Achenbach, 1982). Controversies pervade the mental health professions concerning the classification of severe mental illness, especially in regards to describing how symptoms unfold across development. The first section here provides a historical context for the clinical diagnosis of bipolar disorder in adults as well as in children and adolescents. Additionally, an overview of pediatric bipolar disorder briefly summarizes the assessment, prevalence, course, precursors, and treatment of the illness. A second section is dedicated to emerging phenotypic empirical models that incorporate dimensional approaches to describe and classify mental illness. Third, we briefly describe methods that are currently being explored to classify disruptions in dimensions of behavior and biological substrates that may advance our understanding of bipolar disorder.

Clinical Diagnostic Approaches

Diagnostic Criteria for Bipolar Disorders

The established references for determining the clinical diagnosis of bipolar disorder and other mental illnesses are the *Diagnostic and Statistical Manual* (*DSM*) in the

United States and the *International Classification of Diseases* (*ICD*) in other parts of the world (APA, 2013; WHO, 1992). Although these classification systems are periodically revised, many of the early nosological themes that originally defined bipolar disorder have persisted and continue to be used in clinical practice, as is the case with the recently published *DSM-5* (APA, 2013).

Bipolar disorder (sometimes called bipolar spectrum disorder) collectively refers to the disorders involving manic, mixed, or hypomanic episodes. In the *DSM-5*, bipolar disorders include bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified (NOS), all of which are principally defined by the severity, duration, and frequency of mania rather than the characteristics of depression. In the *ICD-10*, narrower definitions for diagnosing bipolar disorder exist, which exclude bipolar II disorder and emphasize euphoria rather than irritability. The classification system that underlies the *DSM* and *ICD*, the medical model, serves to identify relevant symptoms, criteria for defining syndromes (a group of symptoms that occur together), and disease processes.

Compared with other psychiatric illnesses, bipolar disorder is unique in that it is characterized by two extreme, discrete mood states and accompanying clusters of symptoms, one of which is also found in major depressive disorder. The *DSM-5* primarily distinguishes bipolar disorder from depression on the basis of the presence of manic or hypomanic episodes. Mania, the defining feature of bipolar I disorder, consists of a cluster of symptoms lasting at least 7 days, including abnormally elevated, expansive, or irritable mood; inflated self-esteem or grandiosity; decreased need for sleep; pressured speech; racing thoughts; distractibility; increased goal-directed behavior or psychomotor agitation; and involvement in pleasurable activities that fail to sufficiently account for potential negative consequences (APA, 2013). Mania is associated with impaired functioning, which at times may be severe enough to result in psychosis, hospitalization, or incarceration. By contrast, hypomania (the defining symptom of bipolar II disorder and cyclothymia) involves an abnormally elevated, expansive, or irritable mood that lasts for 4 days with the presence of at least some of the other symptoms that define mania. While hypomanic symptoms must be severe enough to be observed by others, they are not present to the same degree and do not result in the same level of impairment as manic episodes.

Diagnosis of Bipolar Disorders in Adults

Core conceptions of melancholia and mania have been documented since Ancient Greece, beginning with Aristotle, Soranus of Ephesus, and Aretaeus of Cappadocia (reviewed by Goodwin & Jamison, 1990, 2007), and are largely similar to modern diagnostic criteria. Nevertheless, the major breakthrough in the diagnosis and categorization of bipolar disorder came at the turn of the twentieth century. Emil Kraepelin, considered the founder of modern scientific psychiatry, wrote an introductory textbook (1899), in which he described how psychotic illnesses can be differentiated into two categories: (1) manic depressive illness (now referred to as bipolar I disorder); and (2) dementia praecox (now referred to as schizophrenia). Kraepelin viewed manic depressive illness as a manifestation of recurrent endogenous affective illness. This view set the stage for the idea that bipolar disorder and unipolar depression are etiologically related disorders (Angst & Sellaro, 2000). It was not until the 1950s that the distinction between unipolar and bipolar depression gained popularity (Goodwin & Jamison, 2007), and this distinction was not formally incorporated into standard diagnostic criteria until the 1980s (with the *DSM-III*). Alongside the effort to separate bipolar disorder from depression, the subtyping of bipolar disorder became increasingly common in the latter half of the twentieth century, and ultimately led to the first formal classifications of bipolar disorder, cyclothymia disorder, and bipolar disorder NOS as independent subtypes of bipolar disorder in the *DSM-III* (1980). In early conceptualizations, hypomania could be present in cyclothymia disorder or bipolar NOS. The *DSM-IV* (American Psychiatric Association, 1994) introduced the additional category of bipolar II disorder, which was characterized by hypomania (as opposed to the full-blown mania that characterized bipolar I disorder). Although this categorical system has endured in the *DSM-5* (American Psychiatric Association, 2013), there continues to be considerable controversy regarding the characterization of hypomania and the etiological relationship between the different bipolar disorders (e.g., Merikangas et al., 2014).

Diagnosis of Bipolar Disorders in Childhood and Adolescence

Over the last several decades, there have also been important changes to the criteria for the diagnosis of bipolar disorder in children and adolescents. Although there is now undeniable evidence to suggest that bipolar disorder can develop prior to late adolescence or adulthood (Luby, Belden, & Tandon, 2010), the field continues to be fraught with intense controversy regarding the criteria for diagnosing these disorders in childhood and early adolescence. As noted by Goodwin and Jamison (2007), there is an important historical backdrop for these ongoing debates: beliefs about severe mental disorders during the first

half of the twentieth century were heavily influenced by psychoanalytic theory, which focused primarily on adult psychopathology. Disruptions in child development were of relevance primarily as explanatory mechanism for adult psychopathology and garnered little attention on their own behalf (reviewed by Faedda et al., 1995). A full consideration of childhood psychopathology was further hampered by the belief that cognitive developmental prerequisites were necessary for some types of psychopathology to emerge (Glovinsky, 2002). As a result, by the 1960s, there was considerable consensus among mental health professionals that bipolar disorders were limited to adults. This belief was reinforced by a prominent review article published by highly respected scientists who examined the available psychiatric literature between 1884 and 1954 and concluded, "The occurrence of manic depression in early childhood as a clinical phenomenon has yet to be demonstrated" (Anthony & Scott, 1960).

Starting in the 1980s, evidence slowly began to accumulate that refuted the widely held belief that bipolar disorder was exclusively an adult illness. Although there were notable differences in the symptoms of children versus adults, researchers encountered increasing numbers of children whose externalizing and internalizing behaviors were characteristic of adult bipolar disorder (Geller & Luby, 1997). These researchers identified a cluster of symptoms that were largely incompatible with other diagnoses, including elated mood, hypersexuality, grandiosity, and delusional thinking. At the same time, the scientific reports describing the clinical phenomenology of children with manic symptoms highlighted a number of crucial differences between adult and pediatric bipolar symptomatology that incited debate over the application of the diagnosis of bipolar disorder to children. For instance, in a 1997 review, Geller and Luby pointed out that children with manic symptoms most frequently displayed a nonepisodic, rapid-cycling, mixed-manic state and that they frequently exhibited comorbid disorders such as attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD). These diagnoses were subsequently referred to as pediatric bipolar disorder, which attempted to signify the atypical developmental presentation of the disorder in children and adolescents.

There is considerable confusion and controversy as to which criteria are appropriate for use with children and adolescents when defining manic or hypomanic symptoms and episodes. The major issues of the debate are questions about the relationship between child development and mental illness: do the differences between childhood and adult-onset bipolar disorder reflect fundamentally different disorders, or do they share the same genetic and neural underpinnings and differ in presentation for developmental reasons? To address this question, Willcutt and McQueen (2010) identified five competing models of the relation between pediatric-onset bipolar disorder (PBD) and adult-onset bipolar disorder: (1) pediatric BD is not a valid diagnosis; (2) PBD and adult-onset BD are a single developmental disorder; (3) PBD and adult-onset BD are distinct disorders; (4) PBD is a more severe form of adult-onset BD; and (5) individuals with PBD and adult-onset BD both have significant comorbidities which may be best for characterizing the illness and prognosis of BD (for a similar model see Carlson, 2005).

Although it is unlikely that any one of these articulated models will be quickly validated (McClellan et al., 2007), newly emerging evidence regarding the biological, social, and psychological markers of pediatric bipolar disorder are already starting to shape the debate about how to best categorize and diagnose the illness. As outlined by Luby, Belden, and Tandon (2010), three efforts to define pediatric bipolar disorder have received the most attention. One approach typically referred to as a narrow definition for pediatric bipolar disorders entails strict adherence to the *DSM* criteria (e.g., Leibenluft, Charney, Towbin, Bhangoo & Pine, 2003). This approach emphasizes homotypic continuity across development and suggests isomorphic problem presentations in childhood, adolescent and adulthood. That is, this perspective suggests that children with bipolar disorder should have the same symptoms as adults and that these symptoms should not change as the child matures. This model also implies that the etiology of pediatric bipolar disorder is essentially identical to adult bipolar disorder. A second approach involves adherence to the *DSM-IV* criteria with the exception of a shorter duration criteria for mania in children (e.g., Geller et al., 2002). This model also suggests that pediatric and adult-onset bipolar disorders share an identical etiology and course, but stresses that childhood development prevents the expression of sustained episodic moods, which become visible only in adolescence and adulthood. This model attempts to incorporate evidence that many children with mania-like symptoms do not express the well-demarcated mood episodes that characterize adult bipolar disorder and suggests that developmental features should be more fully articulated in the definitions of pediatric bipolar disorder.

The third approach represents a broader definition of pediatric bipolar disorder, with less adherence to *DSM-IV* criteria, and the use of alternative criteria for pediatric bipolar disorder that would include severe irritability

and mood lability, rather than well-demarcated mood episodes (e.g., Biederman, Faraone, Chu, & Wozniak, 1999). Many youth that fit this broader definition of pediatric bipolar disorder may now be diagnosed with the new *DSM-5* disorder called disruptive mood dysregulation disorder (DMDD), which functions as an intermediary between pediatric bipolar disorder and problematic (but not disordered) behavior. DMDD allows children to be diagnosed with a disorder (and thereby receive treatment) who present some characteristic symptoms of mania, particularly severe irritability and hyperarousal, but who lack the well-demarcated mood episodes seen in bipolar disorder (Johnson & McGuinness, 2014; Leibenluft, 2011). By establishing DMDD and leaving the criteria for bipolar disorder largely unchanged (as noted previously the *DSM-5* does not have separate criteria for PDB), the *DSM-5* has largely maintained a strict definition of pediatric bipolar disorder. Further, by classifying DMDD as a depressive disorder rather than with the bipolar and related disorders, the *DSM-5* has responded to preliminary evidence that the two sets of symptoms, albeit similar, have unique etiologies (e.g., Leibenluft, 2011).

Phenomenology of Bipolar Disorders in Childhood and Adolescence

Research to date considering the assessment, prevalence, course, predictors and treatment of pediatric bipolar disorder have been plagued by the definitional controversies described already; some researchers have studied pediatric bipolar populations using a broad definition, whereas others have used a narrow definition. The heterogeneity of the patient populations with pediatric bipolar disorder (e.g., sometimes but not always including prepubertal children) has made it difficult to interpret research on the illness. Nevertheless, the preponderance of available evidence relies on these diagnostic systems (and the varied ways that pediatric bipolar disorder has been defined) and provides a starting point for future research that is more agile at attending to developmental psychopathology principals in understanding the phenomenology of pediatric bipolar disorder.

Assessment. Given the current uncertainty and disagreement over the diagnostic criteria for pediatric bipolar disorder, the development and use of empirically validated, developmentally sensitive assessment tools for children will greatly enhance our understanding of the illness. Currently available assessment tools are limited in that virtually all of them are downward extensions of measures used to assess symptoms or diagnose adults with bipolar disorder. As a result, these measures are often inapplicable to the symptoms of children and do little to enhance our understanding of their thoughts, emotions, and behavior that fall outside of the specific *DSM* or *Structured Clinical Interview for the DSM* (SCID) criteria (Luby, Belden, & Tandon, 2010). This is especially important given that in clinical practice, the clinical interview is the most commonly used approach to assess and diagnose individuals of all ages with bipolar disorder. In research settings, semistructured and structured diagnostic assessments are typically used, with the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS; Kaufman et al., 1997) being the most commonly administered measure to children.

A few assessment measures are starting to use developmentally adjusted criteria. One is the Washington University version of the KSADS, which asks patients for information about symptoms beyond those in the *DSM* but does not require that all symptoms be presented simultaneously to qualify for the diagnosis of a bipolar disorder (Geller et al., 2002). Similarly, the modified Preschool Age Psychiatric Assessment (Luby & Belden, 2006; Luby, Belden, & Tandon, 2010) has developmentally adjusted diagnostic criteria that are designed to distinguish between other common problems (e.g., ADHD). Importantly, there is strong evidence of reliability and validity when narrow definitions of bipolar disorder are used to diagnose adolescents (and potentially children) using these structured diagnostic interviews (Findling et al., 2001; Youngstrom, Birmaher & Findling, 2008).

In addition to diagnostic interviews, questionnaires and checklists may provide information about a range of behaviors relevant to bipolar disorder (as reviewed by Fristad & Algorta, 2013; Johnson, Miller, & Eisner, 2008; Youngstrom, 2007). Some adult checklists that evaluate symptoms of adult bipolar disorder have been applied to children and adolescents, including self-report and parent-report versions of the Young-Manic Rating Scale (Fristad, Weller, & Weller, 1992). Parent and child reports of the General Behavior Inventory (Youngstrom, Findling, Danielson, & Calabres, 2001) have been useful for identifying bipolar symptoms, however, other broad-based psychopathology scales have been shown to address the bipolar phenotype with more limited success (e.g., Bipolar Phenotype of the Child Behavior Checklist; Diler et al., 2009; Faraone et al., 2005). Finally, some specific indexes have been developed including the Child Bipolar Questionnaire, the Child Mania Rating Scale, and the Mood Disorder Questionnaire for Adolescents. Although development of these assessment tools continues, advances in understanding bipolar disorder within the

broader context of psychopathology are likely to inform future measurement tools for pediatric bipolar disorder. Alternatively, Youngstrom (2010) recently proposed an approach to assessment that considers key developmental tasks involved in emotional development and motivational systems. As the field evolves and more is learned about the developmental progression of bipolar disorder, it will be useful to combine the use of more established assessment approaches with more experimental efforts to bridge our understanding of developmental psychopathology of the illness. Many of these themes and controversies inherent to assessment bear out as other aspects of phenomenology are characterized.

Prevalence. Prevalence estimates show that severe mental illnesses such as bipolar spectrum disorder are rare but still represent a significant societal cost (e.g., Kleinman, Lowin, et al., 2003). Although the lifetime prevalence of bipolar I disorder among adults is only around 1.3%, bipolar spectrum disorders occur in 3–7% of the population (Akiskal et al., 2000; Kessler, Chiu, Demler, & Walters, 2005; Soutullo et al., 2005), and are "responsible for the loss of more disability-adjusted life years (DALYs) than all forms of cancer or major neurologic conditions such as epilepsy and Alzheimer's disease, primarily because of its early onset and chronicity across the life span" (Merikangas et al., 2011, p. 241). In contrast to the well-documented prevalence of adult bipolar disorder, there is a dearth of clear epidemiological data on the frequency of pediatric bipolar disorder. Epidemiological studies suggest that pediatric bipolar disorder (ages 6–18) occurs at a rate of between 1 and 2.9%, and subthreshold symptoms occur with a frequency of around 4% to 6% in the United States population, roughly the same prevalence as adult bipolar disorder (Lewinsohn, Klein, & Seeley, 1995; Merikangas al., 2010; Soutullo et al., 2005). In one of the only large-scale epidemiological studies that assessed bipolar disorder in children and adolescents (Kim-Cohen et al., 2003), the rate of bipolar spectrum disorder was 3%. The incidence of bipolar disorder in prepubertal children has not been precisely determined but is thought to be lower than that of postpubertal populations (Ghaemi & Martin, 2007; Luby, Belden, & Tandon, 2010). Although these rates are likely to change as advances are made characterizing bipolar disorder in children and adolescents, they provide a starting point to understand the scope and societal impact of this severely impairing problem.

There are a number of reasons for the difficulty researchers have had in determining the prevalence of bipolar disorder in youth, including methodological limitations, sample identification issues (e.g., complications associated with diagnosing bipolar disorder in youths) and clinical bias (e.g., limitations in developmentally sensitive measures). One major problem has come from the unparalleled rise in the diagnostic rates of bipolar disorder among youth. In a community setting in the United States, there was a 40-fold increase in the diagnosis of bipolar disorder in children and adolescents between 1994 and 2003 (Moreno et al., 2007). This dramatic increase has led many clinicians and researchers to question the validity of the bipolar disorder diagnostic criteria for children (e.g., Leibenluft & Rich, 2008), which has complicated estimates of the disorder's prevalence among youth. Likewise, the sizeable variation in prevalence rates between countries has also undermined efforts to determine the true prevalence of pediatric bipolar disorder. This variance is especially pronounced between the prevalence of pediatric bipolar disorder in the United States and Europe (Soutullo et al., 2005). For instance, American hospital discharge rates for pediatric bipolar disorder were 12.5 times higher than those in England (James et al., 2014). And while the prevalence of pediatric bipolar disorder in an American clinic was 4%, the rate was only 1.2% in Denmark and 1.7% in Finland (Soutullo et al., 2005). As some authors have pointed out (e.g., Stringaris & Youngstrom, 2014; Soutullo et al., 2005), these data do not necessarily mean that the true prevalence of pediatric bipolar disorder varies between countries. Rather, the differences could be due to administrative prevalence such as diagnostic practice, clinician bias against pediatric bipolar disorder in Europe, or overdiagnosis in the United States, and not primarily genetic or environmental factors. Thus, it is still extremely difficult to determine how the true prevalence of pediatric bipolar disorder varies between countries, as each nationality seems to have a unique definition of the illness.

Onset and Course. One key finding is that the onset of bipolar disorder commonly occurs during adolescence and even childhood. In retrospective research studies on adults with bipolar disorder, participants commonly report that problems were first evident in adolescence, and a smaller number report symptoms dating to childhood (Lish et al., 1994; Meyer & Carlson, 2010). Accordingly, two, three, and sometimes four distinct onset ages for bipolar disorder have been identified (Grigoroiu-Serbanescu et al., 2014). One cluster is in midadolescence (age of onset below 18 or 22, depending on the study). A second age of onset is in the mid-20s to 30s. Indeed, most (e.g., 85%) of individuals who will develop bipolar disorder do so before age 35 (Lin et al., 2006). Late onset is typically defined as an onset

after age 35 or 40. Data from prepubescent children are sparse but could potentially represent an additional cluster (see reviews by Bauer et al., 2014; Meyer & Carlson, 2010).

Some researchers are starting to argue that the age of onset is one of the most important clinical features of bipolar disorder, but more studies are needed to show whether each age-of-onset accompanies a unique set of symptoms or even a unique etiology (Meyer & Carlson, 2010). A recent systematic review did not find robust evidence of significant differences in the genetics of early-onset bipolar disorder compared to adult-onset BD, but pointed out that most studies in this field have been underpowered (Kennedy, Cullen, DeYoung & Klimes-Dougan, 2015). Saying that, it has been well-documented that an earlier onset is associated with a worse outcome for the disorder, including greater severity of depression and mania, greater drug and alcohol abuse, greater number of episodes, more rapid cycling, higher suicide rates, and fewer days euthymic (Lin et al., 2006; Post et al., 2010; reviewed by Diler, Birmaher, & Miklowitz, 2010; Luby, Belden, & Tandon, 2010; Meyer & Carlson, 2010). In fact, prepubertal onsets have a poorer prognosis than postpubertal onsets and the adolescent-onset group tends to have poorer functional outcomes than the adult onset group, including higher and more severe rates of psychosis (Perlis et al., 2004) and higher rates of rapid cycling, comorbidity with anxiety, substance abuse, alcohol abuse, and suicide attempts (Lin et al., 2006; Ortiz et al., 2011). One potential cause of the poorer prognosis of early-onset bipolar disorder is its frequent comorbidity with ADHD and conduct disorders (Masi et al., 2006, 2008). There is growing evidence that prognosis is more guarded in the presence of other psychiatric disorders, substance use disorders, and early stress and trauma (reviewed by Goldberg, 2010). This trajectory is largely consistent with core principles of developmental psychopathology that highlight the importance of mastery of developmentally appropriate tasks relevant to cognitive, social, and emotional functioning (Cicchetti & Toth, 1995). Indeed, early failures to master these developmental tasks set a probabilistic course for a more deleterious outcome. Although the etiological relationship between early-onset bipolar disorder, ADHD, and conduct disorders is not fully understood, there is initial evidence that the pediatric bipolar disorder-ADHD subtype represents a distinct disorder with a somewhat independent genetic origin, as will be discussed in the Etiology section of this chapter (Biederman et al., 2013).

In addition to patterns in the onset-age of bipolar disorder, there are also some general patterns that are evident regarding the course of the disorder. For starters, bipolar disorder is an episodic disorder. There is a high probability (70–100%) that children and adolescents with bipolar disorder will recover from an index episode (reviewed by Diler, Birmaher, & Miklowitz, 2010), although only around 40% will return to premorbid functioning levels (reviewed by Goldberg, 2010). The process of stabilization has been found to take about nine months for bipolar I and II (Birmaher et al., 2006).

There is also evidence to suggest that different outcomes are associated with the type of mood episode that individuals first experience. A manic onset tends to have a predominately manic course while a depressed onset tends to have a predominately depressed course. A manic onset typically tends to have a better prognosis than a depressed onset (Forty et al., 2009; Perugi et al., 2000). There is also evidence that the ratio of depressive to manic episodes increases with age (Judd et al., 2002). These data suggest that the etiology of the disorder is more complex and varied than the current diagnostic criteria allow. If anything, one could reason that a manic-onset bipolar disorder would have some notable genetic and neurobiological differences from the depressed-onset bipolar disorder. More research is needed to more fully identify these different subtypes of the disorder (and to identify their relationship to bipolar I and bipolar II disorder).

Manic and depressed episodes are typically recurrent and relapses are common among adolescents and adults with bipolar disorder (as reviewed by Diler, Birmaher, & Miklowitz, 2010). Up to 75% of these youth will experience one or more recurrences within 2 to 8 years after their first diagnosis. Additionally, specific patterns of relapse are evident. For example, youth diagnosed with bipolar I disorder typically have recurring mania or hypomania. Youth diagnosed with bipolar II, cyclothymia or bipolar NOS tend to have more frequently recurring depressive (rather than manic) episodes. It becomes increasingly rare that depression will convert to bipolar disorder through the early to midadult years.

Another major finding from epidemiological research is that the prevalence, onset, course, and prognosis of the disorder differ between males and females (reviewed by Alloy, Abramson, Walshaw, Keyser, & Gerstein, 2006; Baldessarini, Tondo, & Visioli, 2014). In adults, there are no gender differences in the rate of bipolar I disorder, but women are more likely than men to be diagnosed with bipolar II disorder. The course of the disorder also differs considerably for each gender (Baldessarini, Tondo, & Visioli, 2014). Bipolar disorder in women is characterized by a predominantly depressive course, and they are more likely to have a first episode of depression. In contrast,

men are more likely to be characterized predominantly by a manic/hypomanic course and to have a first episode as a manic/hypomanic episode. Bipolar disorder has been found to have an earlier onset in men than in women (Grant et al., 2005), perhaps indicating that gender may moderate prognosis and long-term outcomes. But while men are more likely to have a prepubertal onset, adolescent-onset bipolar disorder tends to affect men and women relatively equally (Birmaher et al., 2009). In adolescence but not adulthood, young men are also more likely to recover from the first manic episode than are young women (DelBello, Hansemann, Adler, Fleck, & Strakowski, 2007). Considerable progress has been made in characterizing bipolar disorder in youth and with refinement of existing conceptualization and assessment practices we are optimistic of the advances that are likely to be made to this current knowledge base.

Prodromes and Precursors. One of the most critical contributions of developmental psychopathology is its emphasis on considering the progression of problems as they unfold across development. A growing number of researchers are using knowledge about the course of bipolar disorder to find ways to detect the onset of the disorder before the major symptoms are apparent. These researchers have employed a number of approaches to detect prodromes of the disorder, and some have proven to be more successful than others. Although one of the most popular is the retrospective identification of prodromes, these approaches are limited in that biases and lapses in memory are likely to significantly influence the findings. To overcome this limitation, some researchers have reviewed medical records to identify early signs of the illness. Better yet are prospective longitudinal research studies, which provide a more definitive approach to identifying the specific prodromes that increase the risk of bipolar disorder. These studies typically focus on groups at high-risk for developing the disorder, including the offspring of bipolar parents and relatives of affected individuals. Most the studies consider childhood or adolescent precursors of adult bipolar disorder and less information is known about the precursors to pediatric-onset bipolar disorder. Although the attention given to prodromes for bipolar disorder has been relatively recent, this work has critical implications for translational efforts. The neurobiological precursors to bipolar disorder will be addressed in Section IV, but in this section we briefly discuss evidence of emotional and behavioral precursors to pediatric and adult-onset bipolar disorder.

Virtually all of the symptoms of bipolar disorder may be evident early in the life span, long before a formal diagnosis of the disorder is made. There is considerable evidence that depression, and to a lesser degree, hypomania is a common precursor of bipolar disorder in adults (e.g., Baldessarini, Tondo, & Visioli, 2014). One retrospective study found that subthreshold manic and depressive symptoms characterizing the prodrome were present for an average of 10 months prior to the onset of adolescent bipolar I disorder (Correll et al., 2014). A chart review of child and adolescent medical records was conducted on bipolar adults (Scott-Gurnell et al., 2014). As children, these adult patients generally manifested a range of symptoms that resembled forms of hypomania or mania. However, elevated mood was not typically part of the presentation; rather, anxiety and irritability were more prominent. Despite the similarity of symptoms, only 23% had been diagnosed with bipolar disorder in childhood. Some of these differences may be attributed to developmental trajectories associated with different types of bipolar disorder (Baldessarini, Tondo, & Visioli, 2014). That is, patients with bipolar II were most likely to present initially with depression (77%) while patients with bipolar I were likely to present initially with depression (46%) as well as psychosis or mania (13 to 22%).

There is growing evidence that both homotypic and heterotypic continuity are evident in bipolar disorder (Rutter, Kim-Cohen & Maughan, 2006). Over the past decade, Duffy and her colleagues have continued to revise a model in which bipolar disorder is shown to evolve through a series of phenotypically different clinical stages for bipolar disorder in adolescence (Duffy, 2010, 2013). These authors proposed a clinical staging model of bipolar disorder, suggesting that the early natural history of bipolar disorder unfolds in a series of predictable clinical stages. In Duffy's (2010) first model, in childhood there was a progression from asymptomatic (well) status to the nonmood disorders (e.g., significant anxiety, sleep, or neurocognitive disturbances such as attention deficit disorder, learning disorders, distortions in reality testing). In adolescence, these problems resulted in minor or major mood disturbances, depression, and eventually mania. Additionally, substance abuse was evident during or after the mood disturbances. Subsequently, these authors have focused more extensively on the role of early anxiety in this developmental progression (Duffy et al., 2013). Most recently, they proposed that offspring of lithium responders are more likely to show the earlier identified progression, in contrast to the offspring of lithium nonresponders who were more likely to have a more varied early course characterized by neurocognitive disturbances and develop psychotic disorders (Duffy et al., 2014). Klimes-Dougan and colleagues have

recently elaborated on key factors of this model that more centrally implicate disturbances in reality testing and other indexes of neurocognitive disturbances. For instance, they have documented differences in thought problems and neurocognitive deficits in offspring of bipolar and unipolar parents (Klimes-Dougan et al., 2006, 2013; Narayan, Allen, Cullen, & Klimes-Dougan, 2013) and evaluated thought problems as precursors of bipolar disorder and other psychotic problems (Klimes-Dougan et al, 2013; Meyer et al., 2004).

Finally, there is growing evidence that youth with bipolar disorder NOS (i.e., subthreshold bipolar symptoms) show a high risk of converting into bipolar I or II disorder. Although hypomanic symptoms in adolescence are common, transient, and typically not predictive of subsequent psychopathology (Tijssen et al., 2010), there is growing evidence that bipolar NOS is a prodrome of pediatric bipolar disorder. One study found that 33% of youth with bipolar NOS converted to bipolar I or II over an 18-month period (Martinez & Fristad, 2013). Another study found that 45% of youth with bipolar NOS converted to bipolar I or II within a 5-year period (Axelson et al., 2011). Although no specific symptom patterns were predictive of conversion, in both studies, a significant family history for bipolar disorder predicted conversion. Nevertheless, given the paucity of longitudinal research that has tracked illness trajectories, these existing models await further revision and elaboration.

Treatment. Intervention research on youth with bipolar disorder has been largely based on traditional phenotypic categorical models of the disorder. There has been considerable controversy around the treatment of these children and adolescents, especially regarding the administration of psychiatric medications to young children (Geller & DelBello, 2008; Luby, Belden & Tandon, 2010). Although substantially less intervention research has been conducted on youths than on adults, the results show some similarities and some differences across development. Unlike psychopharmacological treatment in adults, in which mood stabilizers like lithium or valproate are considered the first-line of therapy (APA, 2002), antipsychotic medications are not typically the first-line medications in children and adolescents. Additionally, antidepressant medications are used in both populations, although there remain concerns about the possibility of antidepressant-induced manic episodes (Correll, Sheridan, & DelBello, 2010). Undoubtedly, more research is needed to determine how to maximize symptom relief while minimizing side effects.

Psychosocial intervention is also highly recommended for youth with bipolar disorder. These interventions are not only essential for minimizing the burden of antipsychotic medications but also for maximizing recovery (e.g., McClellan, Kowatch, & Findling, 2007). Significant progress has been made in the last 10 years in developing and validating psychosocial interventions for bipolar youth (reviewed by Fristad & Algorta, 2013; Miklowitz & Goldstein, 2010). Family-based treatments (e.g., multifamily psychoeducational psychotherapy, family-focused therapy) show the most promise for effectively treating bipolar disorders in youth. There is some evidence noted for individual therapies, including cognitive behavioral therapy, however most other individual therapies (e.g., dialectic behavioral therapy) are currently undergoing efficacy trials and continue to be considered exploratory. Finally, there is growing interest but virtually no empirical support for complementary and alternative treatments (CATs) including supplements of vitamin D and fatty acids. Virtually all of the findings to date are based on relatively small-scale clinical trials. In summary, pharmacological and psychological interventions show some efficacy in the treatment of bipolar disorder in youth. Yet findings often show that remission rates are highly variable, suggesting that the continued development of treatments should be a high priority for this field and that exploring personalization of treatment options may be fruitful.

Empirical Approaches

Dimensional Approaches: Considering Symptoms and Clusters of Symptoms

There are emerging empirical approaches for understanding the broader taxonomic structure of psychopathology and symptom aggregation. It is hoped that these models will help clarify the taxonomic relationship between mental illnesses based on empirical evidence, statistical modeling, and etiology, rather than on consensus among researchers. Empirically based models of illness should enable clinicians to conceptualize, assess, and treat illnesses based on the way specific clusters of symptoms naturally develop, rather than through the artificially defined categories of disorders used by the *DSM* (Krueger & Markon, 2011). In light of the debate over the relationship between pediatric and adult bipolar disorders, these models pose special relevance for the developmental psychopathology of bipolar disorder. Indeed, many empirical approaches were first tested within the context of early developmental psychopathology research. These approaches were only later applied to adult psychopathology, including bipolar

disorders. While these empirical approaches have greatly advanced phenotypic classification systems for behavioral and emotional problems by providing a parsimonious model of symptom patterns, the evidence has not fully determined how well these approaches further the classification of severe mental illness, problems characterized by an episodic course, and symptoms of mania and depression across development.

In the 1970s, Achenbach and colleagues (Achenbach & Edelbrock, 1978) pioneered the use of empirical methods to validate dimensional taxonomies for common childhood emotional and behavioral problems. Their empirical classification approach developed a hierarchical-dimensional model of first-order factors (initially termed *undercontrol* and *overcontrol* but eventually called *internalizing* and *externalizing* behaviors) and second-order factors (e.g., social withdrawal and aggression; Achenbach, 1992). Although some second-order factors loosely mapped onto specific disorders identified in the *DSM* (e.g., conduct disorder symptoms), the model contended that common emotional and behavioral problems existed on a spectrum of internalizing and externalizing behaviors, rather than inside of discrete categories. They also established thresholds demarcating clinical significance for extreme problems and emphasized the value of understanding the full profile of the child's problems rather than any one problem by itself. Thus, this method represents an important early effort to address many of the challenges our current classificatory systems face in categorizing co-occurring problems or comorbid diagnoses. Although these approaches to identifying problem status were initially thought to be most applicable to the developing organism (given the belief that, by adulthood, disease processes were more firmly differentiated and would lead to the symptoms identified in established diagnostic systems; Nottelmann & Jensen, 1998), many now believe that dimensional approaches are equally relevant to adult psychopathology.

It was not until the 1990s that significant progress was made in developing taxonomies for adult disorders that were more encompassing, including those highly relevant to bipolar disorder (e.g., Mineka, Watson, & Clark, 1998). One major advance came from efforts to use quantitative hierarchical models to map the broader array of adult psychopathology along a dimensional spectrum (e.g., Krueger, 1999; Krueger & Markon, 2006). Like the models with children, these hierarchical-dimensional models consist of higher order factors of internalizing and externalizing problems in adults and second-order factors for internalizing problems (distress-based and fear-based problems), rather than the more standard groupings of anxiety and mood problems used by the DSM. This finding with respect to higher order factors has been replicated repeatedly, and the internalizing–externalizing spectrum has become a well-validated tool to model the taxonomic relationship of many common mental illnesses and comorbidities (Kessler et al., 2011). More recently, Krueger and Markon (2011) argued that dimensional-spectrum models of mental illness can also incorporate low prevalence symptoms and complex disorders (e.g., psychosis). In the following section, we discuss more specifically how these models might be relevant to bipolar disorders.

Dimensional Approaches Relevant to Bipolar Disorder

Despite the growing prominence of dimensional-spectrum models of mental illness, most models have focused on common Axis I or Axis I and II symptoms, syndromes, or disorders. In this body of work, the bipolar disorders are generally not represented or underrepresented for a variety of reasons (e.g., the difficulty of assessing mania and psychosis by lay interviews; Kessler et al., 2011; Markon, 2010). As we will summarize, efforts to taxonomically model the symptoms of bipolar disorders have been made using hierarchical and person-centered analytic approaches. The person-centered method of latent class analysis (LCA) assigns individuals to subtypes based on the similarity of their diagnostic profiles. In contrast to factor analysis, LCA can better accommodate phenomena with low base rates.

Consistent with the *DSM* tradition of defining bipolar disorder as a mood disorder (e.g., *DSM-IV*), some researchers have argued that bipolar disorder, particularly the depressive phase of the illness that is predominant for many individuals, fits within the internalizing problem spectrum. Watson revised some of his earlier models and proposed a quantitative hierarchical model for the *DSM-5* which was modified from his tripartite model of depression and anxiety (Watson, 2005). In this model, bipolar disorder had identical loadings on fear, distress and externalizing factor structures, which Watson used to argue that bipolar disorders should be kept as a third diagnosis subclass (along with distress and fear disorders). Keyes et al. (2013) evaluated the meta-structure of Axis I and II disorders using exploratory and confirmatory factor analyses. This study identified a thought disorder factor that, along with fear and distress disorders, was a subdomain of the internalizing dimension. However, both mania and bipolar disorder type I and II exhibited notable associations with the distress and thought disorder subdomains.

Indeed, a growing number of researchers have argued that the bipolar disorder would be more accurately placed in a psychotic or thought disorder spectrum, though they admitted that this placement is far from perfect (Goldberg, Andrews, & Hobbs, 2009; Kotov, Chang, et al., 2011; Kotov, Ruggero, et al., 2011). Some of the most compelling research supporting this position comes from high-risk samples, in which the bipolar disorders are better represented than in epidemiological samples. Kotov, Ruggero, et al. (2011), for example, tested groupings of 25 target disorders on outpatients seeking psychiatric treatment. They found that the best-fitting model of psychopathology was a five-factor hierarchical model composed of internalizing, externalizing, somatoform, antagonism, and, most relevant here, thought disorders (which included psychosis, mania, and cluster A personality disorders). The authors argued that mania shared unique features with these other disorders, including frank psychosis, disorganized thoughts, tangential speech, and bizarre behavior. And like the review by Goldberg, Andrews, and Hobbs (2009), Kotov, Ruggero, and colleagues (2011) admitted that there were notable dissimilarities between the bipolar disorders and the other thought disorders that will require further study. These differences included the negative symptoms of schizoid personality disorder and schizophrenia which are absent in mania, and differences in the early environmental adversities, biomarkers, and course of the disorders. Goldberg et al. (2009) went so far as to argue that bipolar disorder could be viewed as an independent cluster, though the review only compared bipolar disorder to two other disorders, and did little to situate the disorder within the broader range of psychopathology.

Using a person-centered method of latent class analysis, Vaidyanathan, Patrick, and Iacono (2011, 2012) found a five-class model of psychopathology that best fit data from a large epidemiological sample ($n = 5{,}877$). This study was notable for two reasons. Using LCA, the authors largely replicated previous models of externalizing and internalizing (fear and distress) disorders. Second, the authors found that bipolar I disorder is part of a unique cluster of disorders which the authors called the multimorbid class (due to limitations in the epidemiological survey, only bipolar disorder I was considered in the study). This class, representing 3.95% of the sample, also includes the nonaffective psychoses (schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, and others). What sets this model apart from the research discussed above is that the multimorbid class does not fit exclusively within an internalizing, externalizing, or psychotic class, as other researchers posited. Rather, individuals in the multimorbid class had the highest rates of nearly all psychiatric disorders, including most internalizing, externalizing, and psychotic disorders. This helps explain why the bipolar disorders are extremely difficult to classify. While more research and larger samples will be needed to fully clarify the taxonomic placement of the bipolar disorders, current research has shown that the disorders have substantial overlap with other forms of psychopathology and have an unusual relationship to other internalizing and externalizing disorders. Although these models stand in contrast to Kraepelin's (1921) influential clinical observations and dichotomized nosology of manic-depressive insanity and dementia praecox (schizophrenia), they were predicted by early researchers like Bleuler (1924) who emphasized some of the similarities between bipolar disorder and other psychotic disorders. Some exciting new work on the structure of positive emotion will warrant further examination as experience seeking, but not joviality (which is closely linked with life satisfaction), is positively linked with manic and externalizing symptoms (Stanton & Watson, 2014). Further advances in taxonomies and classification serve as a foundation for advancing our understanding of the prevalence, incidence, course, and treatment of bipolar disorders across all ages.

Neuroscience-Informed Approaches to Understanding Psychopathology

Using existing diagnostic classification systems, the field has focused on identifying biomarkers and endophenotypes for bipolar disorder. Biomarkers are measurements that quantify specific biological processes involved in an illness, and they can be used to aid in diagnosis and in tracking disease progress. Ideally, biomarkers would enable clinicians to definitively diagnose an illness by finding neurobiological abnormalities that only exist in one specific disorder. Biomarkers would also have the potential to help revise psychiatric classification systems by defining disorders based on tangible, quantifiable criteria, rather than on the presentation of various symptoms. A review of the available research suggested that mechanisms associated with risk for bipolar disorder may involve abnormalities in frontal-limbic circuitry as well as peripheral biomarkers (e.g., oxidative stress, inflammation and) and genetic biomarkers (e.g., genes involved in calcium ion channels, circadian rhythm, and cell growth; Frey et al., 2013). Some caution is needed in taking this approach, as the use of any individual biomarker is likely to have insufficient explanatory power for susceptibility for bipolar disorders. Despite these important leads, neuroscience research has

come up against some significant challenges in the search for reliable biomarkers of bipolar disorder. One major challenge is that the clinical phenotype is highly complex and somewhat heterogeneous, and it has been difficult to link symptoms and neurobiological abnormalities with their genetic origins. One approach that does not rely primarily on traditional categorical definitions of bipolar disorder is that of endophenotypes. Endophenotypes are conceptualized as intermediates between genes and symptoms or syndromes. They include neurocognitive, neurochemical, neuroanatomical, and endocrine traits that are thought to have a simpler and more specific genetic basis than the whole illness. Gottesman and Gould (2003) identified five criteria that a trait must have to be considered an endophenotype. They contend that an endophenotype is (1) associated with a specific illness; (2) heritable; (3) state independent but age adjusted (i.e., it is still present even when the illness is remitted but it is dependent on the individual's age and development); (4) inherited together with the illness in families; and (5) identified in the relatives of an affected proband at a higher rate than in the general population. Beyond offering researchers more basic, homogenous traits to study (which should have clearer genetic and neurobiological etiologies), endophenotypes could eventually allow clinicians to identify at-risk populations before they experience a mood episode. As discussed briefly later in the chapter, specific neuropsychological deficits in attention, working memory, verbal memory, and executive functioning could constitute possible endophenotypes for bipolar disorder.

Other approaches also do not rely primarily on traditional categorical definitions of bipolar disorder. Recent initiatives have encouraged a shift in new research toward examining dimensions of behavior and underlying neurobiological substrates that characterize features or mental illness, independent of *DSM* diagnoses (e.g., Hyman & Fenton, 2003; Insel, 2009; Morris & Cuthbert, 2012). Major governmental funding in the United States through the National Institute of Mental Health (NIMH) is now supporting and promoting a move to reconceptualize mental disorders within these research domain criteria (RDoC). The goal of RDoC is to enhance understanding of the etiology of diseases and to develop more effective prevention and interventions. RDoC essentially serves to uncouple research from clinically familiar categories to focus on fundamental mechanisms of psychopathology (Sanislow, Pine, Quinn, et al., 2010), though there is little consensus as to how researchers can best do this (Insel, Cuthbert, Garvey, et al., 2010). The NIMH has identified five domains of core relevance and invited the scientific community to measure, develop, and revise these domains to promote scientific advances in this field: positive valence systems, negative valence systems, cognitive systems, systems for social processes, and arousal and regulatory systems. The units of analysis to characterize these domains include genes, molecules, cells, neural circuits, physiology, behavior, self-reports, and paradigms. Although RDoC is a very recent initiative, its underlying philosophy shares some similarities with developmental psychopathology: evaluating multiple units (or alternatively referred to by some as multiple levels) of analysis has been heralded as one of the most important features of developmental psychopathology research (Cicchetti & Dawson, 2002). While these RDoC approaches are just beginning to be applied to research relevant to bipolar disorder (Fristad & Algorta, 2013), existing multidisciplinary research serves as a foundation for identifying the etiology and course of the illness and could help to guide RDoC research on bipolar disorder. An example is work by Urosević, Abramson, Alloy, et al. (2010), who considered an aspect of the positive valence system in their behavioral approach system (BAS) dysregulation model across individuals with more broadly defined bipolar disorders, including bipolar disorder not otherwise specified. These efforts are directed toward more fully understanding larger patterns of atypical functioning across both dimensions of behavior and biology, as well as more specific mechanisms of pathological conditions. With this knowledge, it is hoped that interventions can be developed that more directly target these core disturbances.

ETIOLOGY OF BIPOLAR DISORDER

Like most mental disorders, the specific causes of bipolar disorder are still unknown. However, beginning with the detailed family aggregation patterns observed by Kraepelin, researchers have considered bipolar disorder to be primarily a genetic condition. It has nevertheless been a long journey fraught with many disappointments to identify the specific genetic underpinnings of the illness. No longer saddled with the illusion that simple genetic models can fully account for the course and onset of the bipolar disorders, researchers are now beginning to embrace the complex interactions between development, biology, and environment that affect risk and protection.

Environmental Theories of Bipolar Disorder

Historically, environmental and biological etiological theories of the bipolar disorders have been considered separately, with less emphasis being placed on the environmental causes of the illness. Current models are beginning to acknowledge the critical importance of both environmental and genetic etiological factors, particularly in regard to the role development plays in mediating the interaction of genes and environment. As a prominent researcher noted, only viewing bipolar disorders in biological terms is inadequate in that "genetic and biological processes are unable to fully account for differences in the expression, timing, and polarity of symptoms" (Alloy et al., 2005, p. 1,044). It is now widely accepted that nongenetic factors account for up to 40% of susceptibility to the disorder, and that they play an even larger role in influencing the course, onset, and severity of the illness. Notably, many researchers are starting to recognize the importance of developmental timing; that is, the way environmental and genetic factors interact differently across development. There is also growing interest in how a range of environmental factors impact developmental trajectories, and how these factors affect biological substrates at sensitive periods of development, when brain plasticity is most evident. Thus, despite the current paucity of literature that focuses on the developmental staging of bipolar disorder, we expect that the research on the course of bipolar disorder during the periods of early development (perinatal through toddlerhood) and adolescence will garner increased attention in the near future. In this section we focus on two key environmental factors that can increase risk for bipolar disorder: (1) life stressors, primarily with regard to family dynamics; and (2) environmental hazards.

Life Stressors

There is ample evidence that life stressors play a major role in the onset, severity, and prognosis of several mental illnesses, including bipolar disorder. Elevated stress has been documented in children at risk for bipolar disorder, both in interpersonal and noninterpersonal domains of functioning (e.g., Ostiguy et al., 2009; Radke-Yarrow, 1998). A review of the literature found that 50% of patients recall a major life event preceding their initial episode of bipolar disorder (Johnson & Roberts, 1995), although within the context of bipolar disorder negative life events (e.g., being fired) tend to precede depressive episodes, whereas positive life events (that may also be stressful, e.g., a promotion) tend to precede manic episodes (e.g., Johnson et al., 2008). The connection between life stressors and mood episodes appears to be strongest early in the course of the illness. and there is some evidence to suggest that later episodes of depression and mania are not as closely associated with identifiable life stressors as early episodes (e.g., Hillegers et al., 2004; Post, 2007). In other words, life stress tends to increase risk of bipolar disorder when it occurs at younger ages, though the reasons for this are not yet understood.

There are a host of ways life stressors may affect the onset and course of mental illness. Life stressors may disrupt social rhythms which in turn lead to instability in biological circadian rhythms (Johnson & Roberts, 1995). For example, starting college can upset meal times, bed times, exercise routines and so forth, in additional to the emotional stress caused by the new social demands and more stringent academic requirements. These alterations to circadian rhythms can impact the stability of the endocrine system by deregulating hormone secretion. Indeed, there is considerable evidence that social disruptions are linked to the onset of mood episodes among individuals with bipolar disorder. For example, Boland et al. (2012) reported that, when experiencing life events of the same magnitude and valence, participants with bipolar disorder showed significantly greater levels of disruption in their social rhythms and greater sleep loss compared with normal controls. A number of authors have also found that schedule disruption was associated with an onset of manic symptoms (Boland et al., 2012; Grandin et al., 2006; Malkoff-Schwartz et al., 2000). Although these studies do not necessarily clarify whether social rhythm disruptions cause manic episodes or result from the underlying disorder, the fact that Interpersonal and Social Rhythm Therapy, which helps patients stabilize and regularize social rhythms, is an effective therapy for bipolar disorder suggests that social rhythm disruptions have a causal role in the onset of mood episodes (Frank et al., 2005).

Social support is an environmental factor that may serve to mitigate the effects of life stressors on the course of bipolar disorder. There is evidence that a strong support system may lessen the negative impact of life stressors (e.g., Moon et al., 2014). In the context of bipolar disorder, Greenberg et al. (2014) recently concluded that limited social support is associated with heightened risk for depressive and manic episodes, and that support networks are negatively impacted by manic episodes. One can imagine a vicious cycle in which mood episodes decrease social support and thereby increase the likelihood of additional mood episodes.

Disruptions in the Family Environment. Taking a developmental perspective, the family (and the way family dynamics change over time) provides a particularly important context for considering the impact of early support systems and stressors on the onset and course of bipolar disorder, as well as risk and adaptation. When parents are struggling with their own mental health needs or are overburdened by caring for a child who is suffering from bipolar disorder, they may have limited internal resources to attend to the developmental needs of their child and may thereby intensify the child's risk of psychopathology. It should be noted that the specific ways parents can affect a child's susceptibility to psychopathology are complex and multifaceted because the family is a changing entity that plays different roles across a child's development. Paralleling the concept of normative psychosocial stages in individual development, researchers have explored stages in the life cycle of the nuclear family (Nye & Berardo, 1966; Parsons & Bales, 1955). Weissman, Paykel, and Klerman (1972) identified the primary parenting role of raising an infant as nurturance, of the school-age child as enculturation, of the adolescent as emancipation, and of the young adult as termination of the parental role. While some research to date has focused on environmental risks associated with the first stage of parenting (e.g., attachment), much of research on family risk factors has yet to apply developmentally sensitive approaches or to consider parenting roles as they change over time. It is important to identify the specific developmental stages and ways these parents can increase a child's risk of bipolar disorder. Clinicians would then know the most important periods to help guide parents in caring for their children and diminishing future rates of psychopathology.

The general patterns of family interactions are important to consider because of the evidence that increased stress and deficient social support play a significant role in the onset and course of bipolar disorder. Not only are disruptions in emotion regulation (termed *expressed emotion,* or EE) within the family an important risk factor for severe mental illness, but parents can also model poor emotion regulation and increase their child's susceptibility to the illness (Brown, Birley, & Wing, 1972). The pioneering work by Miklowitz and his colleagues (Miklowitz et al., 1988) pointed to the importance of family processes for bipolar disorder, specifically the role of expressed emotion in families with a history of psychopathology. Specifically, high levels of expressed emotion within families are associated with increased rates of relapse, longer periods of hospitalization, and poor social adjustment in bipolar patients (Miklowitz, 2007; Miklowitz et al., 1988). These findings are particularly important because disrupted patterns of emotion socialization are evident in families at risk for bipolar disorder. One study found that bipolar parents are more likely to respond to offspring's anger with anger (Klimes-Dougan & Harris, 2007). In this same sample, Narayan, Chen, Martinez, Gold, and Klimes-Dougan (in press) found that mothers with bipolar disorder were more likely to have aggressive interactions with their spouses than controls, and the use of these aggressive tactics was associated with the use of aggressive conflict tactics by adolescent offspring when interacting within the family. Other studies have found that low family cohesion and high conflict characterize families with parental bipolar disorder (Chang, Blasey, Ketter, & Steiner, 2001; Moreno et al., 2012; Romero et al., 2005) and families in which a child suffers from bipolar disorder (Belardinelli et al., 2008).

There is also evidence that bipolar parents are more likely to have difficulties creating intimate relationships with their children, thereby increasing their child's risk for bipolar disorder. For example, in prospective observational research using the strange situation, insecure attachment in toddlerhood was found to be more prevalent in offspring of bipolar mothers than in controls (e.g., DeMulder & Radke-Yarrow, 1991; Zahn-Waxler, et al., 1984). This finding has sometimes (e.g., Harnic et al., 2014), but not always, been borne out in retrospective high-risk studies using self-report indexes of attachment among young adults at risk for bipolar disorder (e.g., Doucette et al., 2013). In any case, there is evidence that the capacity for attachment was significantly compromised in adults with bipolar disorder (Greenberg, Rosenblum, McInnis, & Muzik, 2014). Parents can contribute to unhealthy family dynamics in other ways. Elevated reports of physical, sexual, and emotional abuse have been documented in children at high risk for bipolar disorder (Moreno et al., 2012). Abuse histories in childhood, of parents with or without bipolar disorder, have been found to relate to several clinical characteristics of adult bipolar disorder, including earlier age of onset, increased suicidal risk, more rapid cycling, more depressive episodes, more Axis I and II comorbidities, a worse course of illness, and treatment resistance (Etain et al., 2013; Garno et al., 2005; Leverich & Post, 2006).

Despite the host of identified risks associated with poor family dynamics on the onset and course of bipolar disorder, there are a number of characteristics of bipolar families that may promote supportive care and enhance protective factors. Preliminary evidence suggests that bipolar parents may have fewer children than nonbipolar parents (Moreno et al., 2012). Given that bipolar parents

tend to have less stable unions, are more likely to be single parents, and may have primary caregiving roles, having the opportunity to direct their attention to the care of fewer children may be advantageous for both the parent and child's mental health. Additionally, when children at risk for mental illness are co-parented by at least one healthy parent, their risk for psychopathology is diminished (Garcia-Amador et al., 2013). While genetics is certain to play a role, there is also empirical evidence that families have better dynamics when at least one co-parent is healthy (Garcia-Amador et al., 2013). There are also some hints in the literature that critical aspects of parenting may remain highly adaptive. In one study, growing up with a bipolar parent did not result in parents being perceived more negatively unless the young adult was diagnosed with psychiatric problems or bipolar disorder (Reichart et al., 2007). Also when euthymic bipolar adults rated their family of origin, they were perceived to be very similar to that of controls (Cooke, Young, Mohri, Blake, & Joffe, 1999). Overall, recent research reveals the importance of understanding the context of a child's development, including family dynamics, to accurately gauge the impact of risk and protective factors on the onset and course of bipolar disorder.

Developmental Hazards

There are other nongenetic factors that may influence risk and adaptation, including obstetric complications, teratogen exposure, and the seasonal variation in light exposure. While there is evidence that perinatal teratogen exposure and trauma during the birth process play a role in serious psychopathology, their role in the etiology of bipolar disorder has not been fully substantiated. Only very preliminary research is available to determine whether other teratogens such as in-utero exposure to alcohol (O'Connor et al., 2002) or early exposure to heavy metals such as lead or mercury (Pamphlett, 2014) are associated with bipolar disorder. Similarly, there is tentative support for obstetric complications being associated with bipolar disorder. For example, children at high risk for bipolar disorder have more obstetric complications than controls (Moreno et al., 2012). A follow-back study showed that obstetric complications were evident at a higher rate in patients with bipolar disorder than in their unaffected family members (Kinney, Yurgelun-Todd, Tohen, & Tramer, 1998). Retrospective results also suggest that the number of perinatal insults experienced by a child (e.g., drug exposure, birth trauma) increases the prediction of pediatric bipolar disorder (Pavuluri, Henry, Nadimpalli, O'Connor, & Sweeney, 2006). These studies have enormous design challenges that limit the understanding of the short and long-term effects of early exposure to hazards but nevertheless suggest an important area of further inquiry.

Although it is well-established that early childhood exposure to hazards increases the risk of some forms of psychopathology, there remains some question as to whether neurodevelopmental anomalies are associated with elevated risk for bipolar disorder. To more comprehensively address this issue, Murray and colleagues (2004) provided a convincing model that shows that different developmental hazards are involved in schizophrenia and bipolar disorder. Starting from the idea that schizophrenia and bipolar disorder share a common genetic etiology, they identify important environmental factors that are associated with different risk trajectories. They note modest differences in complications in pregnancy and delivery between these two risk groups, with complications being more highly associated with schizophrenia than bipolar disorder. They also identify anomalies in neuropsychological functioning and brain morphology that are most pronounced in those suffering from psychotic disorders. Additionally, some of the assets found to be associated with bipolar disorder (e.g., high IQ and school performance; MacCabe et al., 2010) would be less likely to occur after exposure to early hazards. They conclude that risk for schizophrenia but not bipolar disorder is increased by early insults that impair neurodevelopment. It is possible that hazards may be seen more in those suffering from bipolar disorder than in controls, but the highest risk for hazard exposure is associated with schizophrenia. Nevertheless, teratogen exposure later in adolescence and early adulthood may also be a risk factor for bipolar disorder, as the brain continues to undergo development during those periods. Here, the evidence generally mirrors that for schizophrenia and other psychotic disorders. While it is not clear if cannabis use increases the overall risk for bipolar disorder (as evidence shows for schizophrenia), cannabis use has been associated with an earlier age of onset for bipolar disorder and a worse prognosis (Gonzalez-Pinto et al., 2008; Lagerberg et al., 2011, 2014). In these studies, however, it is still not clear if cannabis use causes a worse prognosis or if greater cannabis use results from a more severe form of the disorder.

A host of other potential hazards that are currently being researched may also contribute in small but additive ways to our understanding of the etiology of bipolar disorder. Seasonal variation and light exposure patterns have recently been suggested to represent environmental hazards for those at risk for the disorder. There is some support for a theory that the springtime increase in solar

sunlight (insolation) is associated with an earlier age of onset (Bauer et al., 2012). Also, among patients diagnosed with bipolar disorder, there is a modest preponderance of births in the winter and spring months (Torrey, Miller, Rawlings, & Yolken, 1997). This insolation factor has been found to be especially important for those at high family risk for mood disorders and for initial depressive episodes as opposed to initial manic episodes (Bauer et al., 2014). Stability of the light–dark cycle is important in maintaining circadian rhythms, stimulating vitamin D synthesis, and regulating moods and may warrant further consideration as an etiological factor in bipolar disorder. Some researchers have also suggested that dietary habits and microbial agents could also increase susceptibility to severe mental illness by potentially impacting neural functioning and increasing oxidative stress (reviewed by Yolken & Torrey, 2008).

Overall, this research remains preliminary, but may deepen our understanding of the diversity of environmental factors that can increase risk for bipolar disorder. While environmental hazards do not account for most cases of bipolar disorder or cause the disorder by themselves, efforts to develop complex models of how stage-salient hazards might interact with other environmental stressors and genetics are needed to enhance our knowledge of risk and protective factors for bipolar disorder and to develop intervention strategies that can minimize the impact of these environmental hazards. The interplay between environmental, developmental, and genetic factors continues to be an important focus of research. We believe that this multi-modal focus is the best strategy to fully explicate the causes of bipolar disorder.

Biological Theories of Bipolar Disorder

Behavioral Genetics

Historically, family studies have served as a foundation for behavioral genetics research and can be divided into family risk studies and adoption studies. In a basic sense, these studies help determine the overall heritability of a disorder, the specific phenotypes that appear to be independently heritable, and the environmental factors that can increase susceptibility to a disorder. Despite the advances of molecular genetics and the methodological challenges associated with this highly heterogeneous and relatively rare disorder, family risk studies continue to provide some of the most robust, consistent, and novel findings about the heritability of the bipolar disorder. Family risk studies relevant to bipolar disorder fall into two major categories: twin studies and proband relative identification. There have been relatively few adoption studies on bipolar disorder, so they will not be discussed in this section. They generally support the primarily genetic basis of bipolar disorder (see Goodwin & Jamison, 2007, for a more extensive review).

Twin studies evaluate how often monozygotic twins (sharing nearly 100% of DNA) or dizygotic twins (sharing roughly 50% of DNA) are concordant or discordant for a characteristic of interest. The data obtained from these studies have conclusively shown that monozygotic twins are at a significantly higher risk of developing bipolar disorder than dizygotic twins, when one twin has the illness (Kato et al., 2005; Smoller & Finn, 2003). According to one study of 67 twin pairs in the United Kingdom, heritability estimates were found to be 89% (Craddock & Sklar, 2008). Other studies indicate that the monozygotic twin of a bipolar proband has a lifetime susceptibility of 40–70%, about 60 times the rate of the general population (Craddock & Jones, 1999; Craddock & Sklar, 2013; Smoller & Finn, 2003; Tsuang & Faraone, 1990). Concordance rates between monozygotic twins were typically between 5% and 10%, very similar to that of nontwin siblings (Smoller & Finn, 2003). The findings from twin studies suggest that bipolar disorder has one of the highest genetic susceptibility rates of any mental illness (Shih, Belmonte, & Zandi, 2004). Indeed, having a family member who is diagnosed with bipolar disorder is the best-known predictor of bipolar disorder in both children and in adults. Twin studies, especially longitudinal twin studies, also have the potential for advancing our understanding of the risk and protective factors for bipolar disorder. For instance, when only one co-twin has the disorder, researchers can investigate whether any specific unshared environmental factor may have increased or decreased susceptibility. The recent trends toward multisite collaborations in twin studies offer a positive sign that this approach will play a prominent role in the future of psychiatric genetics.

The second major type of family risk study evaluates the rates of bipolar disorder in relatives of a proband. Given the relatively low incidence of bipolar disorder, the most commonly-used family risk study design involves recruiting all available first-degree relatives of a proband for participation in the study. Occasionally, a more restricted approach is used to identify extreme risk populations that involve multiple family members diagnosed with bipolar disorder (e.g., Maziade, Rouleau, Gingras, et al., 2009). Family proband studies do little to model the developmental progression of bipolar disorder, but like twin studies, the results of family-proband studies have been robust and consistent in asserting the high degree of heritable susceptibility to bipolar disorder. Whereas the

lifetime prevalence of bipolar disorder (strictly defined) is around 1% of the general population (Merikangas et al., 2011), the most recent and comprehensive familial studies have shown that first-degree relatives of a proband have a lifetime prevalence of 5–10%, around eight times the rate of the general population (Craddock & Jones, 1999; Craddock & Sklar, 2013; Lichtenstein et al., 2009). Taken together, these studies have led to heritability estimates (the proportion of total phenotypic variation caused by primarily additive genetic factors) ranging from 0.59 to 0.93 (Bienvenu, Davydow, & Kendler 2010; Kieseppa et al., 2004; Lichtenstein et al., 2009; McGuffin et al., 2003), though some researchers have suggested that heritability estimates often discount shared and unshared environmental factors (Bentall, 2009). Finally, it is also possible that family risk studies considering unaffected individuals in middle and older adulthood may characterize a resilient sample and can be used to identify risk and protective factors for the disorder (Frangou, 2011).

Offspring studies are a specific type of family risk studies which focus on the offspring of parents (one or both) with bipolar disorder. Offspring are considered high risk because they are likely to incur risk both from environmental and genetic contributions (between 4 and 15% will develop bipolar disorder, compared with 0- 2% of offspring of healthy parents) (Birmaher et al., 2009; Lapalme, Hodgins, & LaRoche, 1997). Due to the fact that a sizeable proportion of offspring will develop bipolar disorder and that the peak age of onset is between 16 and 30 years (the majority of individuals who will develop bipolar disorder will do so before they are 25 years old; Merikangas et al., 2011), studying offspring before the age of highest risk is a powerful way to evaluate risk progression and identify precursors of the illness by using prospective longitudinal methodology that carefully addresses variation in development (e.g., Meyer et al., 2004; Radke-Yarrow, 1998).

Offspring studies also provide a broader understanding of risk and resilience. Consistent with principles of multifinality, only a minority of offspring of bipolar parents will develop bipolar disorder, but up to 40–50% of the offspring of parents with bipolar disorder (O-bipolar disorder) will develop other moderate to severe forms of psychopathology during childhood and adolescence (Birmaher et al., 2009; Lapalme, Hodgins, & LaRoche, 1997). There is also some preliminary evidence to suggest that the onset of emotional and behavioral problems may be delayed in offspring of bipolar parents relative to other risk groups, although by adolescence the rates of psychopathology in offspring of bipolar and unipolar parents are comparable (Klimes-Dougan et al., 1999, 2006). Other longitudinal evidence uses repeated measurement approaches to identify differential developmental trajectories of low-incident, highly deleterious outcomes including suicide (Klimes-Dougan, Free, Ronsaville, Stilwell, Welsh, & Radke-Yarrow, 1999) and disturbances in reality testing (e.g., Klimes-Dougan et al., 2013).

While family, twin, and offspring studies have been typically used to document the primarily genetic etiology of bipolar disorder, these studies are increasingly being used to identify the importance of specific environmental factors that increase susceptibility to bipolar disorder (e.g., Brietzke et al., 2012; Johnson, 2005). For example, the fact that concordance between monozygotic twins is noticeably lower than 100% indicates that both shared and unshared environmental effects play a significant role in susceptibility to the disorder, with Lichtenstein and colleagues providing evidence that unshared environmental factors have the more substantial influence (Lichtenstein et al., 2009; Uher, 2014).

Family and twin studies have also shown that the heritability of bipolar disorder is more complex and multifaceted than was originally thought. In particular, these studies offer compelling evidence that the different bipolar disorders have unique genetic underpinnings and that many of the common symptoms and comorbidities that accompany bipolar disorder have an independent genetic etiology. For instance, a number of family and twin studies indicate that bipolar II disorder is a highly heterogeneous disorder that often has a tenuous genetic relationship to bipolar I disorder (Barnett & Smoller, 2009; Smoller & Finn, 2003). They also show that many symptoms and comorbidities of bipolar disorder have a genetic basis (that is often independent of the genetic basis of bipolar disorder). These include specific comorbidities like alcohol abuse and phenotypic features like suicidality, rapid-cycling, lithium-responsiveness, and psychosis (see Barnett & Smoller, 2009; Craddock & Sklar, 2013). Family studies have also documented a large shared genetic etiology between bipolar disorder and schizophrenia, and to a lesser extent, between bipolar disorder and major depression (e.g., Lichtenstein et al., 2009; McGuffin et al., 2003)

Of particular importance to developmental psychopathology, family risk studies are beginning to clarify the genetic etiology of pediatric bipolar disorder. For example, Wozniak and colleagues (2012) found that the odds ratio for bipolar I disorder in first-degree relatives of a proband was 6.96 and that relatives of a bipolar youth were 4 to 14 times more susceptible to bipolar disorder, compared with relatives of a nonbipolar disorder proband. Although these authors argued that pediatric

bipolar I disorder is a valid diagnostic entity that is directly related to adult-onset bipolar I, others have suggested that pediatric bipolar disorder is an independent homogenous subset of adult bipolar disorder and as such does not predominately share the same genetic profile (Faraone, Glatt, & Tsuang, 2003). Additionally, there have been questions about the relationship between ADHD and bipolar disorder in children and adolescents for some time. Though some researchers note that bipolar disorder and ADHD must have common genetic elements based on the high frequency of the comorbid disorder (ranging from 70 to 98%) and their similar phenotypic presentation (Schimmelmann et al., 2013), some recent accounts have found that pediatric bipolar I disorder, ADHD, and *comorbid* pediatric bipolar disorder–ADHD independently breed true in families, meaning that each disorder has a largely unique genetic origin (Biederman et al., 2013). This line of research is important because, although the results remain tentative at best, they represent efforts to consider etiological contributions to pediatric bipolar disorder rather than relying on the assumptions that downward extensions of adult pathology models are relevant to youth.

Molecular Genetics

While family and twin studies continue to be an important and oft-used tool to assess the heritability of bipolar disorder, over the past 25 years, molecular genetics research has become the dominant paradigm in psychiatric genetics research. Perhaps more than most other fields, progress in genetics research has been inextricably tied to technological advancements, whose breakneck pace has led to rapid and dramatic paradigm shifts in the field. These advances have dramatically refined our understanding of the etiology of most psychiatric illnesses. While early family studies led researchers to search for a few bipolar genes that followed a Mendelian pattern of inheritance, newer research has shown that complex psychiatric disorders are caused by thousands of genetic variants, the majority of which only marginally increase one's risk of a disorder (Craddock & Sklar, 2013). Recent research has also definitely outlined the shared genetic etiology between many common psychiatric disorders and are beginning to show how development and the environment interact with genes to increase or decrease susceptibility to an illness. Although the most advanced molecular genetics methods have currently identified only a small number of bipolar-risk genes, researchers have now identified more potentially profitable directions to uncover the causal genetic elements that underlie bipolar disorder.

Linkage Studies. Before the advent of high-powered, computationally driven association studies, geneticists relied on lower resolution techniques. The first of these was the gene linkage study, which gained prominence in the 1990s. Linkage studies typically use pedigrees from 10 to 100 large families with multiple affected individuals and are most effective when used to identify rare gene variants with relatively large contributions to the susceptibility of a disease (Craddock & Sklar, 2013). In essence, they are used to find positional candidate genes by narrowing the major areas of genetic susceptibility from the entire genome to specific chromosomes and chromosomal regions (Juli, Juli, & Juli, 2012). Although more than 40 linkage scans for bipolar disorder have implicated a handful of chromosomal regions, these results have largely been conflicting, inconsistent, and unreplicated (Barnett & Smoller, 2009). The most comprehensive meta-analysis specifically implicated chromosome 6q, 8q, and 9p (McQueen et al., 2005). A recent review of linkage studies identified 15 other candidate regions that have been implicated in bipolar disorder, but acknowledged that there is little cross-study reproducibility of these findings (see Juli, Juli, & Juli, 2012). These findings suggest that bipolar disorder is instead likely caused by many common genetic variations, each of which having a small additive effect on overall susceptibility that would be too small to observe with linkage studies. Linkage studies have dwindled in popularity as researchers have reasoned that the thousands of genes involved in bipolar disorder will require more powerful and precise tools than linkage studies can provide.

Candidate Gene-Association Studies. The increasing evidence that bipolar disorder was caused by a large number of genes with small effects has caused a paradigm shift in psychiatric genetics over the last 15 to 20 years. Advances in molecular genetics allowed for gene-association studies, in which researchers could identify specific common variations with small effects. Gene-association studies were originally used to study candidate genes based on evidence from chromosomal regions identified in linkage studies, post-mortem examination of brain tissue, as well as existing models of neurobiological anomalies (Barnett & Smoller, 2009; Craddock & Sklar, 2013). Many candidate gene studies on bipolar disorder have focused on genes involved in serotonin transporters and receptors (SLC6A4 and HTR2A), catechol-O-methyl transferase (COMT), brain-derived neurotrophic factor (BDNF), tryptophan hydroxylase 1(TPH1), D-amino acid oxidase activator (DAOA or G72), neuregulin (NRG1), and disrupted in schizophrenia (DSC1 and DSC2) (Juli et al.,

2012; Seifuddin et al., 2012), but these studies have primarily yielded negative, inconsistent, and irreproducible findings (see Szczepankiewicz, 2013 for a more in-depth review). A recent meta-analysis reviewed 487 candidate gene studies and did not identify a single significant finding after correcting for multiple testing (Seifuddin et al., 2012). Candidate–gene association studies have very rarely examined pediatric bipolar disorder. One available study, although underpowered, failed to show a connection between candidate genes and the disorder, including for BDNF, SLC6A4, and COMT (Mick et al., 2009).

The results of these studies indicate that our current biological understanding of the disorder is either incorrect or incomplete. In retrospect, the failure of gene-candidate studies is not entirely surprising (see Barnett & Smoller, 2009; Craddock & Sklar, 2013; Seifuddin et al., 2012). Candidate gene studies (along with linkage studies) are methodologically flawed because they are premised on the limited etiological validity of current classification systems as well as our incomplete understanding of the neurobiology of a disorder. Although it is possible that some candidate genes still play a role in bipolar disorder as rare variants or types of genetic variations not captured by gene-association research, at a minimum, they suggest that the disorder's neurobiological mechanisms are far more complex and multifaceted than is currently believed, and likely involve a large number of genetic factors and distinct neurological pathways (Seifuddin et al., 2012).

Genome-Wide Association Studies. The next major advance in genetics research, genome-wide association studies (GWAS), allowed researchers to identify susceptibility genes without relying on a priori hypotheses about candidate genes. This meant that GWAS could identify new genetic variants involved in bipolar disorder and create new etiological hypotheses based purely on data from gene-assays, without any need for prior theories of the disorder's neurobiology. Put simply, GWAS use micro-chip gene assays to selectively genotype tens of thousands of individuals and correlate their genotype with phenotypic data, thereby showing which variants are involved in an illness. GWAS largely focus on single-nucleotide polymorphisms (SNPs), which are variants in the individual nucleotides that make up genes (although the gene-assays can also be used to identify some structural variants). A SNP typically represents one version of a gene (an allele) with a unique impact on an individual's phenotype. GWAS attempt to pick up on this (modest) association, although in the future GWA studies may be able to achieve larger sample sizes and use gene-assays with greater resolution to study the role of low frequency and rare SNPs in psychiatric disorders (Gratten et al., 2014). Most common SNPs have fairly small effects and do not dramatically affect one's phenotype, but the combined effect of thousands of small SNPs can be significant. The popularity of genome-wide association studies has resulted from major advances in genotyping (and statistical analysis) which have increased their resolution, and dramatically lowered their cost.

Despite the successes of GWAS with a handful of diseases (e.g., breast cancer, Crohn's disease, diabetes, cystic fibrosis), novel findings from GWA studies have not progressed as quickly as researchers originally expected, especially for complex heterogeneous polygenic disorders like mental illnesses. With regards to bipolar disorder, most GWAS have only found a small handful of genes involved in the disorder. The largest GWA study to date included nearly 12,000 individuals with bipolar disorder and over 50,000 controls and identified only two loci with genome-wide significance, the cell surface protein gene ODZ4 and the calcium ion channel subunit gene CACNA1C (Psychiatric GWAS Consortium-Bipolar Disorder Working Group, 2011). Other genes that have been commonly implicated by GWAS include other calcium ion channel subunits (e.g., CACNA1D and CACNB3; PGC-Bipolar Disorder Working Group, 2011) and cell-surface or extracellular matrix proteins involved in inter-cellular communication (e.g., ODZ4, ANK3, NEK4-ITIH1,3,4, and NCAN). As Scott and colleagues (2009, p. 7,505) stated, many of the results from GWAS indicate that "subtle differences in neural development or neuroplasticity may underlie mood disorders," although the specific neurobiological functions of the genetic variants identified by GWAS are not fully understood (Cichon et al., 2011; see also Craddock & Sklar, 2013; Szczepankiewicz, 2013).

These early GWA studies have also served to enhance our understanding of the relationship between different mental illnesses and the heterogeneity of patients diagnosed using *DSM* criteria (Doherty & Owen, 2014). For example, researchers recently found that the genetic correlation of SNPs between schizophrenia and bipolar disorder is 0.68 ($\pm$0.04) and that the correlation between bipolar disorder and major depression is 0.47 ($\pm$0.06), suggesting that there is major etiological overlap between the different disorders (CDG-PGC et al., 2013). SNP-based calculations also determined that individuals diagnosed with bipolar disorder form a relatively heterogeneous group, with SNP correlations ranging from 0.55 and 0.88 for individuals diagnosed with a bipolar disorder (CDG-PGC et al., 2013). These results reinforce a number of family and twin studies which found minimal explicit connection

between bipolar I disorder and bipolar II disorder and raise questions about the validity of current categorical diagnostic criteria, like the *DSM* or *ICD*. Despite the ability of GWAS to help determine the etiology of a disorder, there have been very few GWA-related studies on pediatric bipolar disorder and their results not been very significant. The few that we could locate were typically underpowered or unconventional. Rather than attempting to find novel SNPs among a pediatric bipolar population, they typically searched for the presence of SNPs that had already been implicated in adults within a small pediatric bipolar sample (e.g., Schimmelmann et al., 2013). Although amassing a large pediatric bipolar population will be difficult, a true GWA study could definitively show the relationship between pediatric and adult-onset bipolar disorder.

In spite of the value of these findings, the discrepancy between the heritability of a disorder estimated by family studies and the relatively small number of genes identified by GWAS has been a source of disappointment and contention (this problem is referred to as missing heritability). The issue of missing heritability has led some researchers to ask whether alternative forms of genetic variance underlie bipolar disorder (and other complex polygenic illnesses) that cannot be identified by GWAS. Recent statistical software called Genome-wide Complex Trait Analysis (GCTA) has provided answers to this question. GCTA allows researchers to compute the proportion of heritability that is caused by common SNPs (Lee & Chow, 2014; Yang, Lee, Goddard, & Visscher, 2011). GCTA indicates that 23–27% of the variance in liability of bipolar disorder is caused by thousands of common SNPs with small effect sizes (schizophrenia has been estimated to involve 8,300 SNPs which are responsible for up to 50% of the *genetic* variance) (CDG-PGC, 2013; Ripke et al., 2013). This means that the other proportion of genetic variance is caused by rare SNPs and structural variants (including copy number variants) that are too infrequent to be identified by the current gene-arrays and sample sizes used. The findings from GCTA are tremendously important because they affirm the idea that GWAS, however disappointing thus far, are the correct tool to determine a large portion of the genes involved in complex mental illnesses. The disappointing results of GWA studies are not due to the absence of common SNPs in the etiology of these illnesses, but due the fact that their sample sizes are simply too small to identify the tiny contributions of thousands of independent polymorphisms (Gratten et al., 2014). When researchers are able to gather extremely large numbers (hundreds of thousands) of bipolar participants, the results are likely to be similar to recent, ground-breaking research on schizophrenia. One study employed more than 36,000 subjects and 113,000 controls and identified over 120 SNPs from 108 independent loci (Schizophrenia Working Group of the PGC, 2014; Gratten et al., 2014). Indeed, among the well-studied mental illnesses, there is a clear correlation between the number of loci identified and the sample sizes used in the studies (Gratten et al., 2014). Although amassing such large samples may take a decade or longer to accomplish, intersite collaborative efforts have already proven successful in gathering large subject pools (e.g., the Psychiatric GWAS Consortium and the Wellcome Trust Case Control Consortium).

Future research on psychiatric genetics will also be better able to identify rare variants (discussed in the next section) with moderate-to-large effect sizes through new technological advances (e.g., next-generation sequencing or full-genome sequencing; Cruceanu et al., 2013). The current DNA microarrays that are used to identify common SNPs are unable to tag very rare variants (primarily structural variants and uncommon SNPs), which are responsible for a sizeable proportion of genetic liability for bipolar disorder. When the cost of genome sequencing falls far enough, gene-association studies using whole genomes will become perhaps the predominant tool used to identify rare variants. Likewise, whole exome-sequencing (high-throughput DNA sequencing), which evaluates only the protein-coding portion of the genome (the exome) is being increasingly used as a technique to identify rare and de novo variants using smaller sample sizes. While little is known about the significance of exomic variation in bipolar disorder, this approach has shown some promise when applied to other serious mental illnesses like autism (Gratten et al., 2014). In the coming decade, it is hoped that researchers will be able to quantitatively determine the role of rare SNPs and rare structural variants in the mental illness, as has been done with common SNPs.

Structural Variation and Copy-Number Variants. Structural variations refer to genomic inversions, translocations, and copy-number variants (CNVs; insertions and deletions). In contrast to sequence variations (single nucleotide variations in a string of DNA), structural variants are large-scale changes in the organization of DNA, ranging from alterations to a few kilobases to changes in many megabases. As mentioned already, structural variants tend to be very rare (with a frequency of less than 0.001) and have fairly large effects (between 2 and 20 times the effect size of common SNPs; Gratten et al., 2014). This section will focus primarily on copy number variants, as CNVs have been the most studied form of structural variation in

psychiatric genetics. These variants are receiving increased attention in the study of complex mental illnesses due to evidence that common SNPs explain only about a quarter of total genetic liability. Researchers reason that rare CNVs (and rare SNPs) with large effect sizes must therefore be responsible for a large portion of genetic susceptibility not already accounted for by common SNPs, as rare variants would not be tagged by the microarrays currently used in GWAS. Although the specific contributions of CNVs are largely unknown and are likely to vary considerably between different illnesses (Gratten et al., 2014), CNVs have already been implicated in illnesses like velocardiofacial syndrome, intellectual disability, schizophrenia, and autism (Kirov et al., 2014; Malhotra & Sebat, 2012). Theoretically, CNVs (and rare SNPs) should become easier to identify as newer genotyping assays and larger sample sizes are used, as is the case with rare SNPs (Gratten et al., 2014).

With regard to bipolar disorder, only a small handful of studies have evaluated the role of CNVs and current findings have been mixed. While a few studies have identified a small number of CNVs which appear to occur in both bipolar disorder and schizophrenia, (Lee, Woon, et al., 2012), other investigators found that CNVs were far more frequent in individuals with schizophrenia compared with individuals with bipolar disorder or controls (Grozeva et al., 2010). Given that CNVs have been linked to cognitive deficits, and cognitive deficits are more highly associated with schizophrenia than bipolar disorder, it has been hypothesized that the greater cognitive impairment in schizophrenia is more closely linked with CNV anomalies. Other groups of researchers have found evidence that a type of CNV, called singleton deletions, occur more frequently in individuals with bipolar disorder than in schizophrenia, but these results have not been replicated (Rucker & McGuffin, 2012).

Though preliminary, there have also been a few promising findings from CNV studies with direct relevance to developmental psychopathology. First, one study found evidence that CNVs occur more frequently in early-onset bipolar disorder (before 21) compared with the adult-onset disorder (after 21), suggesting that there is a unique genetic etiology to the early-onset disorder (Priebe et al, 2011). A second study found that de novo CNVs (structural changes which spontaneously appear in a child's DNA and are not found in her parents) are more common in early-onset bipolar disorder (Malhotra et al., 2011). This result is especially intriguing when we consider two other findings from recent studies. First, there is evidence that de novo CNVs are influenced by environmental factors, like parental age (in the case of bipolar disorder) and maternal nutrition (in the case of schizophrenia) (Frans et al., 2008; Lee et al., 2012). In fact, the age of onset of bipolar disorder has been found to be earlier in offspring of older fathers, especially for women and families with little history of mental illness (Grigoroiu-Serbanescu et al., 2012). One would expect to see a higher rate of *de novo* mutations in older fathers because their spermatogonial cells are continually replicating and continually introducing new mutations. Second, a number of studies have found that CNVs play a crucial role in neurodevelopmental disorders like intellectual disability and autism (Girirajan et al., 2011; Gill, 2012), indicating that there could be a unique connection between early-onset bipolar disorder and genes that affect neurodevelopment. Taken together, these pieces of evidence affirm the idea that environmental circumstances can directly affect the genetic basis of bipolar disorder and that the early-onset of bipolar disorder may have a genetic etiology that is closely related to other neurodevelopmental disorders. In a larger sense, some researchers argue that rare CNVs (especially *de novo* CNVs) may cause each instance of psychiatric illness to have a unique genetic etiology (Malhotra & Sebat, 2012). This would suggest that attempts to class disorders by etiology may be an extremely difficult enterprise, and would raise questions about the possibility of treating mental illness if each case is caused by a different set of rare variants. In total, research on the role of CNVs in bipolar disorder has been limited but promising, and certainly warrants further study (see Malhotra & Sebat, 2012, for a more general discussion of the role of CNVs and rare variants in psychiatric genetics).

Nonadditive Genetic Mechanisms

While the heritability estimates derived from family studies reflect mainly additive genetic factors, there are other genetic mechanisms that could play a role in the onset of the illness. We now turn our attention to the two most researched alternative genetic mechanisms that are likely to hold some explanatory value for the etiology of bipolar disorder, gene–environment (GxE) interactions, and epigenetics. Both domains of research accept the idea that the environment can modify an individual's genetic susceptibility to illness. But while GxE researchers attempt to find specific risk genes that can be activated by particular events, epigenetics research investigates the ways that environmental experiences can affect how the genotype is expressed. Stated another way, epigenetics research aims to find the mechanism of gene–environment interactions, and not simply the genes involved. Other nonadditive genetic mechanisms, like epistasis (gene-gene interactions) are growing in importance, but are beyond the scope of this

chapter. We will conclude by examining the oxidative-stress model of bipolar disorder in an effort to show how genetic theories of bipolar disorder can be integrated with current neurobiological research.

Gene–Environment Interactions. In a basic sense, current GxE associational studies are very similar to candidate gene-association studies (discussed previously) in that they attempt to find a correlation between a particular population sample and specific preselected genetic variant. In this case, the sample populations include individuals with bipolar disorder who have and have not experienced certain environmental influences, like childhood abuse, cannabis use, or life stressors. Much of this research is an extension of a substantial body of literature which documents how specific environmental influences can increase or decrease the risk of mood-disorders, including childhood trauma, life stressors, and social support (e.g., Brietzke et al., 2012; Johnson, 2005; Miklowitz & Johnson, 2009). In a larger sense, gene–environment research has been stimulated by evidence that genetic factors were only partly responsible for the disorder (e.g., the discordance between monozygotic twins or the fact that heritability estimates are substantially lower than 100%) but still caused distinct patterns of symptoms that were related to environment influences, like the relationship between bipolar disorder and childhood-sexual abuse.

Since the first major paper on psychiatric GxE interactions (Caspi et al., 2003), there has been a tremendous interest in the field, followed by considerable controversy and heated debate about the acceptability of these approaches, particularly when using SNPs (Burmeister, McInnis, & Zöllner, 2008). The most positive findings have come from epidemiological data which show a clear correlation between neural changes, childhood stress, and knowledge that bipolar disorder is highly heritable. For instance, researchers have documented significant neuronal variation between individuals with and without bipolar disorder who have been subject to childhood trauma like physical or sexual abuse. This evidence indicates that individuals with bipolar disorder have a genetic susceptibility to the disorder that can be triggered by childhood trauma, leading to unique pathophysiological changes in the brain (Brietzke et al., 2012). These studies also suggest that GxE are highly dependent on an individual's development. Many of the neurological changes triggered by environmental stress vary dramatically with age, meaning that there is a specific window of neural development which increases a child's vulnerability to stress (Brietzke et al., 2012). Therefore, bipolar disorder not only appears to be influenced by gene–environment interactions, but also by gene-environment-development interactions which can heighten susceptibility to the disorder at certain ages, but not at others. In fact, a recent study by Miller and colleagues (2013) has given preliminary evidence of a gene–environment–development interaction involved in bipolar disorder with the brain-derived neurotrophic factor (BDNF) val66met genotype could exacerbate the effects of childhood sexual abuse on the severity and chronicity of bipolar disorder (Miller et al., 2013). Other researchers have demonstrated that the serotonin transporter gene 5-HTTLPR polymorphism increases the rate of recurrent (rather than single-episode) depression when individuals have experienced childhood stress (Uher et al., 2011). Importantly, these studies reveal a threefold connection between genetic predisposition, environmental stress, and development as risk factors for bipolar disorder. Still, the results of gene–environment studies have been fairly inconclusive when researchers have sought to identify *specific* GxE interactions by using candidate gene-association studies (cGxE). As with conventional candidate-gene association studies, researchers have not encountered anywhere near the number of GxE interactions that they originally expected. This is likely due to the fact that the majority of genetic variants involved in bipolar disorder have very small effects, making identification in cGxE studies quite difficult, especially when current cGxE studies do not use a developmental perspective to inform their genetic theories (Vrieze, Iacono, & McGue, 2012).

Epigenetics. In its contemporary usage, epigenetics refers to chemical changes to the genome that do not affect the specific ordering of DNA nucleotides but alter gene expression (the process by which a DNA sequence is used as a template for protein production). This typically occurs in two ways. First, epigenetic modifications be covalent modifications of the DNA bases themselves (typically methylation) which affect the ability of DNA to be transcribed and expressed. Methylation causes genes to become silenced or underexpressed, while demethylation and hypomethylation cause genes to be expressed or overexpressed. Second, epigenetic modifications can occur to the histone proteins that make up the larger organized structure of DNA, called chromatin. Enzyme-guided processes like the methylation, acetylation, and phosphorylation of histones can affect how tightly the DNA in a cell is packed. When DNA is packed very tightly, genes cannot be expressed and are effectively turned off.

Although the mechanisms of epigenetic modification are not completely understood, there are a few major features that make it an important subject of genetics research on bipolar disorder. First, epigenetic modifications affect the expression of an individual's genotype without actually altering her DNA sequence. This means that even if someone has a gene that predisposes her to an illness, that gene could be silenced by epigenetic modification and could not meaningfully affect her phenotype. Second, unlike an individual's genome which is permanent and unchanging (except in the case of very rare mutations), epigenetic modifications can frequently occur as a result of environmental influences. For instance, researchers have observed changes in the methylation (and expression) of genes that affect drug-seeking behavior after administering cocaine to subjects (Kumar et al., 2005). Although the expression of DNA can also be affected by environmental influences (e.g., stress causes the release of cortisol which affects the expression of genes), these effects are usually transient. By contrast, environmentally induced epigenetic modifications can be long-lasting and persistent, especially if they occur early in development (Bredy, Sun & Kober, 2010). In some animal models, epigenetic modifications that occur in childhood persist into adolescence and adulthood (Kofink et al., 2013; Meaney 2010). Despite our limited understanding of the mechanisms and significance of epigenetic modifications in humans, environmentally induced epigenetic modifications hint at the complexity of molecular biology and complicate our current understanding of psychiatric genetics.

Within the past ten years, a surge in research on epigenetics has demonstrated that epigenetic modifications are likely to play a role in many psychiatric illnesses, including bipolar disorder. Researchers have shown that a handful of genes involved in bipolar disorder are affected by epigenetic alterations. These include peptidylprolyl isomerase E-like (PIPIEL) which is involved in dopamine transmission and the neuroendrocrine system; brain-derived neurotrophic factor (BDNF); the serotonin receptor 5HTR1A; the regulation of DNA methyltransferases, which are involved in epigenetic DNA methylation; the HLA complex group 9 gene (HCG9), which is thought to play a role in stress response and neuronal death; and catechol-O-methyltransferase (COMT) genes (see Bredy, Sun, & Kobor, 2010). By either methylating or demethylating these genes, epigenetic modifications are correlated with an increased susceptibility to bipolar disorder (though it is not clear to what extent), presumably because they increase the effects of genes that are involved in the disorder. This hypothesis is supported by the physiological mechanisms of drugs that reduce the symptoms of bipolar disorder. The mood stabilizer valproate, for instance, inhibits the enzyme histone deacetylase, thereby reducing gene expression (Kato et al., 2005). Other effective bipolar medications, like S-adenosyl methionine (SAM), appear to increase DNA methylation and reduce gene expression (Kato et al., 2005). It is notable that the preliminary epigenetics studies show a clear concordance with GWAS findings, suggesting that epigenetic modifications and genotypic susceptibility go hand-in-hand. That is, the genes that seem to be affected by epigenetic modifications are genes that have been implicated by GWAS, and these epigenetic modifications appear to cause the overexpression of risk genes and the underexpression of protective genes, like BDNF. But because researchers have largely only studied candidate genes, like those identified by GWAS, it is not clear how epigenetic modifications affect the thousands of other genetic variants involved in the disorder.

The most exciting feature of epigenetics research is the connection between environmental influences, epigenetic modifications, and development. Researchers have recently shown that epigenetics is a dynamic process whereby environmental stresses can effectively turn susceptibility genes on or off, including genes for behavioral traits related to mood disorders. For example, genes involved in drug use, vulnerability to stress, anxiety, and fear-related learning and memory can be epigenetically modified by environmental influences like early-life trauma and intense stress (Bredy et al, 2010). This means that an environmental trigger could be necessary to activate susceptibility genes for a psychiatric disorder, like bipolar disorder. In other words, epigenetics could be responsible for the widely observed connection between environmental influences and genetic predisposition to an illness (e.g., Miller et al., 2013). Indeed, epigenetics could be one major reason why there is a fairly substantial discordance rate between monozygotic twins for psychiatric illnesses, as researchers have shown that monozygotic twins have very different genome-wide epigenetic patterns by the time they reach adulthood (Bredy et al., 2010). Although these twins have the same genes, the way these genes are actually being expressed is quite different. Other researchers, however, have proposed that de novo copy number variants could also be responsible for this phenomenon (Malhotra & Sebat, 2012).

Crucially, there is strong evidence that epigenetic modification of susceptibility genes are highly influenced by

an individual's development. There appears to be critical periods of brain development where certain genes can be epigenetically modified, with repercussions that last into adolescence and adulthood (Kofink et al., 2013; Pishva et al., 2014). Although much of this evidence has come from research with animals or through indirect research on humans (and should therefore be cautiously applied to the developmental psychopathology of bipolar disorder), the findings are still provocative. For example, researchers have shown that the level of maternal care in young mice is associated with epigenetic modification of genes involved in the hypothalamic-pituitary-adrenal (HPA) axis, which plays an important role in stress-management and depression. These early-life epigenetic modifications caused changes in gene expression and behavior that lasted into adulthood (see Pishva et al., 2014). By contrast, adolescent or adult mice exposed to similar stressors (like lack of maternal care) would not experience epigenetic modifications to their DNA. Research on children has indicated that humans have a similar developmental window where environmental stressors can cause long-lasting changes in gene expression, due to epigenetic mechanisms. A handful of studies on humans have illustrated a connection between childhood trauma and epigenetic modifications which persist into adolescence and adulthood, and ultimately increase susceptibility to psychiatric illness (Pishva et al., 2014). Taken as a whole, these studies help to elucidate the etiology of bipolar disorder and suggest that determining its genetic origins will require more than the identification of SNPs. Instead, these studies suggest that the environment can interact with an individual's genes in a manner that is sensitive to stages of human development. New research in epigenetics aims at bridging the gap between animal-research and work on humans. Advances in biotechnology and molecular biology are slowly starting to allow for genome-wide epigenetic profiling of individuals with bipolar disorder, which should help to elucidate the prevalence and importance of epigenetic modifications in the disorder. Although epigenetic research on psychiatric illnesses is promising, much more work is still needed to be done before we understand the role of epigenetic modifications in the etiology of bipolar disorder.

Oxidative Stress. One recent model of bipolar disorder shares similarities with the two models of gene–environment interactions discussed earlier, and suggests that bipolar disorder is influenced by oxidative stress in the brain. Put simply, oxidative stress refers to the activity of reactive oxygen species (typically generated in cells as byproducts of metabolism), which can degrade cellular macromolecules like proteins and DNA, trigger cell-death, and result in epigenetic modifications to DNA (see Andreazza, 2012). It should be pointed out that research on oxidative stress differs from research on GxE interactions and epigenetics because it does not typically attempt to pinpoint specific genes or environmental interactions which can increase susceptibility to bipolar disorder. Oxidative stress is not a field of genetics research but rather one model of the way that genes and environmental influences can interact in a complex manner. If models of oxidative stress continue to be supported by research, it seems likely that researchers will search for genes that contribute to oxidative damage.

The two major models of oxidative stress include the theory of Allostatic Load (AL) and the theory of accelerated aging (AA), both of which contend that certain psychiatric illnesses are a result of long-term neurodegenerative damage from oxidative stress caused by long-term environmental stressors and genetic susceptibility (Rizzo et al., 2014; for a developmental psychopathology perspective on allostatic load see Cicchetti, 2011). Proponents of these theories cite findings from post-mortem evaluation of brain tissue and neuroimaging studies which indicate that oxidative damage is heightened in individuals with bipolar disorder, leading to many of the same physiological and neurocognitive impairments seen in normal patterns of aging (e.g., shortened telomeres, slowing cognition, reduced brain weight and volume, and cardiovascular conditions; see Rizzo et al., 2014). Although the literature on oxidative stress and psychiatric illness is still relatively small, it could signal an important future direction for the field. The most advanced theories of oxidative stress are multi-causal and multi-disciplinary: they suggest a complex interaction between genetic vulnerability to oxidative damage, environmental stressors that increase oxidative stress, and specific periods of neural development (Rizzo et al., 2014). And in contrast to current etiological models which portray bipolar disorder as a cyclic disease, many models of oxidative stress and accelerated aging contend that bipolar disorder is a progressive disease with symptoms that change over time. Rather than treating bipolar disorder as a static illness, these models indicate that bipolar disorder will have vastly different profiles as the illness progresses, and may require unique strategies for treating it at different stages in the life span.

NEUROIMAGING FINDINGS IN PEDIATRIC BIPOLAR DISORDER AND HIGH-RISK POPULATIONS

Bipolar disorder has widely been characterized as a neurodevelopmental disorder and accordingly, research in

the neural mechanisms of bipolar disorder represent an important domain of discovery. Before neuroimaging technology was available for the study of the brain there were a range of methods that were used to study brain functioning in bipolar populations. Early efforts to understand the morphology and cytoarchitecture of the brain involved postmortem evaluations. Although this methodology has still not been applied to the study of pediatric bipolar disorder, contributions of this work was important. For example, research in adults showed evidence of subtle volumetric differences in regions hypothesized to contribute to the pathogenesis of mood disorders such as basal ganglia, locus ceruleus, and dorsal raphe, (reviewed by Baumann & Bogerts, 2001). Additionally, electroencephalography (EEG) research on bipolar disorder was initiated in the 1950s. Some of the important contributions of this work include evidence of asymmetry in bipolar patients (Clementz, Sponheim, Iacono, & Beiser, 1994). This research showed that patients with bipolar disorder demonstrated heightened right hemisphere activity, consistent with hypotheses concerning nondominant hemisphere involvement in the regulation of elated mood. Finally, research assessing neuropsychological functioning has made major contributions to our understanding of bipolar disorder. Cognitive impairments have been consistently identified in patients with bipolar disorder on measures of attention, working memory, verbal memory, and executive functioning (e.g., cognitive flexibility; reviewed by Quraishi & Frangou, 2002; meta-analysis by Lee, Hermenst, et al., 2014), with these deficits generally evident in the euthymic state (meta-analysis by Arts et al., 2007; Bora et al., 2009; Mann-Wrobel, Carreno, & Dickinson, 2011; Robinson et al., 2006; Torres et al., 2007). Research examining neuropsychological functioning in children and adolescents with bipolar disorder shows a remarkably similar, although not always as robust a pattern of deficits as those of adults (reviewed by Horn, Roessner, & Holtmann, 2011; Joseph et al, 2008). There is also evidence that identified functional deficits in some of these neurocognitive tasks may precede the onset of bipolar disorder. For example, deficient functioning has been noted in relatives of bipolar probands (Arts et al., 2007; Bora et al., 2009; Robinson et al., 2006) and offspring of bipolar parents (Klimes-Dougan et al., 2006). Most notably, there is preliminary evidence that the presence of executive functioning deficits and working memory impairments in at-risk offspring of bipolar parents can predict the later onset of bipolar disorder (Meyer et al., 2004). At the same time, Savitz, Solms, and Ramesar (2005) identified a number of studies that did not find cognitive or academic impairments in youth who went on to develop BD, though measure of academic performance may not be an appropriate measure of impairments in verbal memory or executive function. Nonetheless, some of these well-established methodologies will continue to provide a critical role in advancing our understanding of the pathophysiology of bipolar disorder for they provide complementary information with the more recently-used imaging technologies that now allow scientists to view the workings of the brain in real-time.

There has been considerable progress in recent decades in the ability to examine the neural underpinnings of psychiatric illness through the application of various types of brain imaging techniques. The majority of neurobiological research has focused on adults diagnosed with bipolar disorder, with research approaches including more invasive brain imaging technologies (e.g., positron emission tomography and CT scans) that have limited application in youth because of radiation exposure, for instance. The focus of this section will be on the advances relevant to developmental neurobiology and psychopathology using exclusively noninvasive imaging technologies, much of which have taken place in the past decade. This research has begun to identify the aberrant neural circuits that are implicated in bipolar disorder, shedding light on the pathophysiology of the disease and providing the foundation for conceptualizing treatments that could be targeted to impact abnormal circuitry. In this section we will first review neuroimaging findings in pediatric bipolar disorder (organized by imaging modality). We will then describe how pediatric bipolar findings differ from other psychiatric populations. A discussion of developmental trajectories will incorporate an examination of findings differentiating pediatric bipolar from adult bipolar disorder, results on at-risk populations, and longitudinal results. Finally, we review the extant research examining how existing treatments impact abnormal circuitry in youth with bipolar disorder before discussing implications for the future. A detailed summary of the available, but limited, research is provided.

Volumetric/Morphometry Studies

The most cumulative neuroimaging data on bipolar disorder in children and adolescents is available from studies that have used high-resolution T1-weighted images to measure the volume of brain structures. Similar to the general pattern of findings in adults, many of these studies have implicated key frontolimbic structures such as the amygdala, hippocampus, basal ganglia, and cortical regulatory regions, reflecting abnormalities in the circuitry which is thought to subserve emotion regulation, memory and motivated behavior (Phillips et al., 2003).

Amygdala

Several studies have found that youth with bipolar disorder have smaller amygdala volumes than healthy controls (Chen et al., 2004; DelBello et al., 2004; Dickstein et al., 2005; Kalmar et al., 2009). Recent reviews and meta-analyses suggest that decreased amygdala volume is more consistently observed in youth than in adults with bipolar disorder (Pfeifer et al, 2008; Savitz & Drevets, 2009; Usher, Leucht, Falkai, & Scherk, 2010). One study found that while left amygdala size was positively related to age in a sample of bipolar youth ranging from 10 to 21 years of age, the healthy control group showed an inverse relationship between amygdala size and age (Chen et al., 2004). In addition, a meta-analysis of studies that examined amygdala volumes in children, adolescents, and adults with bipolar disorder reported that children and adolescents with bipolar disorder had significantly smaller amygdala volumes than typically developing children, whereas amygdala volumes in adults were nonsignificantly larger than the healthy adults (Pfeifer et al., 2008). Taken together, it appears that there may be a developmental trajectory in youth with bipolar disorder in which early on, patients have abnormally small amygdala volumes, but over time, while their healthy counterparts show a trajectory of decreasing amygdala volume, bipolar youths' amygdala volumes increase.

Hippocampus

Savitz and Drevets (2009) recently conducted a comprehensive review of studies examining neural circuits implicated in mood disorders and found that, in contrast to MDD, in which hippocampal volumes are consistently smaller (particularly in chronically, severely depressed older adults), there were no differences in hippocampal volume in patients with bipolar disorder. However, in the pediatric literature, several studies (but not all [Chen et al., 2004]) have found smaller hippocampal volumes in samples of youth with bipolar disorder. In a study of 43 youths with bipolar disorder and 20 healthy controls, Frazier and colleagues reported smaller hippocampal volumes in the bipolar disorder group, which was driven predominantly by the female subjects (Frazier et al., 2005). In a multimodal analysis of 18 children with bipolar disorder in the manic phase and 18 matched controls, Gao and colleagues found decreased gray matter volume in the left hippocampus in the patient group (no sex effects were reported), which was inversely related to manic symptoms as measured by the Youth Mania Rating Scale (Gao et al., 2013). Bearden et al (2008) focused on the three-dimensional morphology of the hippocampus. They found decreased hippocampal volumes in bipolar disorder youth compared with case controls. Specifically the subiculum region of the hippocampus was the region most implicated. Interestingly, this region has projections to the prefrontal cortex (PFC) and thus may represent some disturbances in frontotemporal neurocirciutry. In addition to a possible link with manic symptoms, it is conceivable that lower hippocampal volumes in pediatric bipolar disorder could underlie the memory deficits seen in this group (Joseph et al., 2008), although this link has not been directly studied.

Other Subcortical Regions

In contrast to abnormally low amygdala volumes in pediatric bipolar patients, studies have found increased volumes of basal ganglia regions (e.g., putamen, caudate, globus pallidus) and thalamus in youth with bipolar disorder compared with controls (Adleman et al., 2012; DelBello et al., 2004; Wilke et al., 2004). However, one study found reduced volumes of the left nucleus accumbens in youth with bipolar disorder compared with controls (Dickstein et al., 2005). In contrast, a recent examination of basal ganglia structures in adults with bipolar disorder found volume reductions in the globus pallidus and putamen, but no group differences in the nucleus accumbens or thalamus (Womer et al., 2014). The heterogeneity of findings across studies could reflect the small samples that are typically used for imaging studies and may reflect developmental changes due to a different mix of age-groups in each study. This hypothesis would require longitudinal measurement to examine change in basal ganglia volumes with maturation in those with versus without bipolar disorder. Implication of these brain areas, which are known to be involved in generating positive affect, may provide some clues as to the emergence of manic symptoms in youth with bipolar disorder.

Cortical

In addition to the subcortical regions discussed above, various studies have reported that in comparison to healthy controls, pediatric patients with bipolar disorder have smaller volumes of cortical areas such as the left dorsolateral PFC (Dickstein et al., 2005), frontal, temporal parietal and occipital lobes (Frazier et al., 2005; James et al., 2011), as well as smaller gray matter in medial temporal lobe and orbitofrontal cortex (Wilke et al., 2004) and in the anterior cingulate cortex (Gao et al., 2013; Wilke et al., 2004). These deficits have been linked with impaired cognitive functioning in working memory, executive function,

language, and verbal memory (James et al., 2011) and may underpin some of the reduced capacity for emotion regulation in youths with bipolar disorder.

Functional MRI

Numerous studies have now used functional magnetic resonance imaging (fMRI) to examine brain functioning in youth with bipolar disorder. A common approach has been to utilize an experimental paradigm in which participants view emotional faces, and the blood-oxygen-level-dependent (BOLD) signal associated with the task is examined in patients versus control groups. A larger BOLD signal reflects greater blood flow to specific regions of the brain and therefore increased brain activity in that region. Kim and colleagues (2012) evaluated youth and adults with bipolar disorder and healthy controls using an fMRI task that presented angry, fearful, and neutral faces. Compared with healthy controls, both pediatric and adult bipolar samples showed greater activation in the right amygdala in response to fearful faces. When more global patterns of response were evaluated that included responses to all emotional stimuli, only the youth with bipolar disorder showed excessive activation in the right amygdala. Another fMRI study tested a facial expression task on youth with bipolar spectrum disorder, a matched nonbipolar clinical group, and a control group. Compared with the other two groups, the bipolar spectrum group showed lower fusiform activation when viewing facial expressions across a range of emotions, suggesting deficits in the visual processing brain regions (Perlman et al., 2013). Whole-brain analyses have also been conducted on euthymic adolescent patients with bipolar disorder and healthy controls when viewing emotional facial expressions (Garrett et al., 2012). In this study, the bipolar disorder group showed lower dorsolateral prefrontal cortex activation but greater amygdala and hippocampal activation. Limbic hyperactivation was observed in youth with bipolar disorder using another face viewing paradigm (Rich et al., 2006). Youth with bipolar disorder rated neutral emotion faces as more hostile than the control group, and showed greater activation in the amygdala, nucleus accumbens and other brain regions when rating how hostile the face appears or how much fear they experienced. Although some of the youth in bipolar disorder group were euthymic, within-patient group differences were not observed. Together, these studies suggest that limbic hyperactivity to negative emotion may be trait-related rather than state-related for youth with bipolar disorder. More recently, Adleman and colleagues (2013) reported that children with bipolar disorder exhibit impaired memory for emotion faces as well as elevated fusiform activation during the processing of these faces. Since the fusiform cortex is known to be critical for the processing of face information, it may be that increased activation in patients reflects a greater neural demand to accomplish the task in comparison to controls. Further, Adleman et al. reported that elevated fusiform activation was correlated to manic symptoms, suggesting it may represent a state and trait biomarker of bipolar disorder in children.

Another application of fMRI is to measure functional connectivity. Since functionally connected regions have synchronized resting-state BOLD signal (Biswal, 1995), comparing BOLD signal across different brain regions can be used to estimate brain connectivity within networks of interest. Two studies have been published to date using resting-state fMRI to assess brain connectivity in youth with bipolar disorder. Wu and colleagues used an automated method to examine resting-state functional connectivity across the entire brain (Wu et al., 2013). They identified three networks, an affective network, an executive network, and a sensorimotor network. In youth with bipolar disorder ($n = 34$), the affective and executive networks had greater involvement of the dorsal anterior cingulate cortex (ACC), than that seen in controls ($n = 40$). Dickstein and colleagues examined functional connectivity in 15 youth with bipolar disorder and 15 controls, and reported that the patient group had greater negative connectivity between left dorsolateral PFC and right superior temporal gyrus than the control group (Dickstein et al., 2010). Another study examined regional homogeneity (ReHo), which is a data-driven approach for examining resting-state data that measures connectivity between nearby regions throughout the brain, in 15 adolescents with bipolar disorder versus 15 healthy controls (Xiao et al., 2013). Patients showed lower ReHo than controls in several cortical areas, but greater ReHo in several limbic areas. Furthermore, elevated limbic ReHo was correlated with manic symptoms. Functional connectivity can also be examined using a task, rather than the resting state. Two studies utilizing an emotion face task have documented reduced frontolimbic connectivity in adolescents with bipolar disorder compared with controls (Rich et al., 2008; Wang et al., 2012).

In yet another application of fMRI, researchers can measure the amplitude of low frequency fluctuations (ALFF) of resting-state BOLD signal. This measure has been shown to be highly correlated with cerebral blood flow (Zou et al., 2009). Lu and colleagues (2014) applied this method in a sample of pediatric bipolar patients

(predominately bipolar I disorder). Compared with the control group, patients showed significantly lower ALFF in left precuneus, left superior parietal lobule, and bilateral inferior occipital gyrus, but greater ALFF in the bilateral caudate and left pallidum. Additionally, there was a significant positive correlation between the ALFF value of the left pallidum and level of manic symptoms, suggesting that increased baseline neural activity in this region may be important for generating mania.

In summary, the extant research using fMRI to examine neural circuitry in pediatric bipolar disorder have utilized very different approaches but have broadly implicated abnormalities in cortical-limbic circuits in these young patients. These findings shed light on how regional brain dysfunction manifests at a network level in these patients. Future research using more uniform methods and larger samples is needed to support and extend these early findings.

Neuroimaging Assessment of White Matter

As has been found in adults with bipolar disorder (Tighe et al., 2012), early research examining white matter in pediatric bipolar disorder using T2-weighted images noted elevations in white matter hyperintensities (areas of increased signal which are thought to reflect a brain abnormality that could have numerous etiologies) in these patients (Botteron et al., 1995; Pillai et al., 2002). However, more recent and expanded work looking at 35 affected and 45 unaffected offspring of parents with bipolar disorder along with 40 healthy controls found that the proportion of low-grade white matter hyperintensitites was similar across groups (Gunde et al., 2011). Nevertheless, interest in white matter as a key part of the pathophysiology of bipolar disorder in youth and adults has continued and, with the advent of more advanced technologies such as diffusion tensor imaging, has led to some progress in understanding of the disorder.

In the past decade, several studies have applied diffusion tensor imaging (DTI) to examine white matter in pediatric patients with bipolar disorder. DTI measures the diffusion of water, and provides an estimate of whether water molecules can diffuse freely (isotropic movement) or if they are restricted in their movements (anisotropic movement), as in the case of a barrier such as an axon. Greater limitation of white matter diffusion is therefore suggestive of a greater degree of white matter microstructure imposing a limitation to diffusion of water molecules. In general, these studies have all indicated lower fractional anisotropy (FA), an indicator of white matter integrity, in the patient group compared with controls. This general finding is thought to be a reflection of greater disorganization of the white matter connections in the brain, which might subserve some of the deficits in emotion regulation and impulse control in these patients. Common locations of low fractional anisotropy include the corpus callosum, internal capsule, and cingulum. However, the location of white matter deficits has varied across studies, suggesting that the abnormality may not necessarily be specific to circuits involving emotion regulation.

In the first DTI study of pediatric bipolar disorder, Frazier and colleagues (2007) examined 10 children with bipolar disorder, 8 healthy controls, and 7 at-risk children with a first-degree relative with bipolar disorder. The bipolar disorder group showed lower FA than both other groups in cingulate and paracingulate white matter. In addition, patients showed lower FA than controls in right and left superior frontal tracts, left orbitofrontal white matter, and right corpus callosum body. Both patients with bipolar disorder and the at-risk groups had lower FA than controls in the superior longitudinal fasciculus bilaterally (Frazier et al., 2007). In a study of 13 children and adolescents with pediatric bipolar disorder, 13 children with ADHD and 15 healthy controls, Pavuluri and colleagues (2009) reported that both patient groups had lower FA in the anterior corona radiata. Also, the ADHD group had lower FA in the anterior limb of the internal capsule and the superior region of the internal capsule in comparison to both other groups (Pavuluri et al., 2009). Barnea-Goraly and colleagues examined 21 adolescents with bipolar disorder who were also the offspring of a bipolar parent and 18 age and IQ matched healthy comparison participants. Adolescents with bipolar disorder had lower FA values than controls in the fornix, left midposterior cingulate gyrus, corpus callosum, in fibers extending from fornix to thalamus, and in parietal and occipital chorona radiata bilaterally. There were no correlations between FA and clinical measures (Barnea-Goraly et al., 2009). Saxena and colleagues found lower FA in the genu of the corpus callosum and in the anterior commisure in 10 youth (aged 7–17) with bipolar disorder versus 10 healthy controls. In the patient group, FA values were negatively correlated with a lifetime history of aggression (Saxena et al., 2012). James and colleagues assessed youth diagnosed with bipolar disorder with psychosis (age 11–18) and found decreased FA was in the anterior corpus callosum. These changes were associated with differences in cognitive functioning (James et al., 2011). One limitation that is common across many bipolar studies is that the patients are frequently medicated, raising the potential confound that differences

in neural structure and function are due to the medication and not the disorder. A recent study suggests that this may be an important issue. It examined white matter integrity in 18 unmedicated children and adolescents with bipolar disorder and 18 controls, and found no significant group differences (Teixeira et al., 2014).

In summary, DTI studies to date of pediatric bipolar disorder have been fairly small in size. They have generally suggested impaired white matter integrity, but there has not been a consensus on the location of the abnormalities. Few studies have been able to identify within-patient group correlations with dimensions such as symptom severity, limiting conclusions about the biological meaning of the findings. Given the ongoing development of white matter during adolescence (e.g., Giedd, 2004; Paus, 2010), it is important to recognize that there may be a wide variation in white matter integrity (among both sample and control groups) that may make the identification of clinically relevant abnormalities more difficult, even with closely matched control samples.

Spectroscopy

Magnetic resonance spectroscopy (MRS) is a technique that measures the concentration of a range of neurometabolites in specific areas of the brain. MRS can provide additional insight into the state of the brain in vivo that complements other imaging methods. Several MRS studies have been used in cross sectional designs to investigate biomarkers associated with bipolar disorder. These studies typically measure a standard set of neurometabolites within hypothesized regions of interest. The following summarizes key findings according to the neurometabolite that was measured.

N-acetyl-aspartate (NAA)

NAA is thought to be a marker of neuronal density and viability. Reduced NAA could reflect abnormal dendritic arborization and neuropil, supporting a neurodevelopmental hypothesis for the pathophysiology of bipolar disorder. Most, but not all (Patel, DelBello et al., 2008) studies of pediatric bipolar disorder have found lower NAA in patients than controls. A study of 15 children and adolescents with familial bipolar disorder (offspring of one or two parents with bipolar disorder) and 11 healthy controls examined neurometabolites in the dorsolateral prefrontal cortex (DLPFC). This study reported lower NAA levels in the right DLPFC, but no differences in myoinositol or choline levels, two other commonly studied neurometabolites (Chang et al., 2003). In another study, Cecil and colleagues reported a trend for lower NAA and creatine levels in the cerebellar vermis in 9 children aged 8–12 years with bipolar disorder in comparison to 10 group-matched healthy controls (Cecil et al., 2003). Sassi and colleagues (2005) reported lower NAA in the dorsolateral prefrontal cortex in in 14 adolescents with bipolar disorder (mean age 15.5) in comparison to 18 healthy comparison subjects using MRS. They also reported that NAA levels were negatively correlated with number of previous episodes. In a larger study, Olvera and colleagues reported lower NAA in the left dorsolateral prefrontal cortex in 35 children and adolescents with bipolar disorder (mean age 13.2) in comparison to 36 matched healthy controls. Furthermore, it appeared that the finding of low NAA was primarily driven by the early puberty group as opposed as to the children in other developmental stages (Olvera et al., 2007). Another relatively large MRS study was conducted on 43 children with bipolar disorder (mean age 13.2) and 38 healthy controls. The authors reported that the patient group had lower concentrations of NAA and choline-containing compounds in bilateral medial prefrontal cortex, and lower creatine compounds in the left medial prefrontal cortex. They also found lower NAA and creatine compounds in left DLPFC white matter (Caetano et al., 2011). In contrast, in a study of 28 adolescents with bipolar depression versus 10 controls, Patel and colleagues found greater concentrations of NAA in the ACC and bilateral ventrolatral PFC in the bipolar disorder group compared with controls (Patel, DelBello et al., 2008).

Choline-Containing Compounds

Choline-containing compounds provide information about cellular membrane integrity. Patel and colleagues found increased left ventrolatral PFC concentration of choline in 28 adolescents with bipolar depression in comparison to controls (Patel, Cecil et al., 2008). Caetano et al. reported that in their study of 43 children with bipolar disorder and 38 previously described healthy controls, patients showed lower concentrations of choline-containing compounds in bilateral medial PFC (Caetano et al., 2011). However, Chang and colleagues reported no differences in choline levels in the right DLPFC in their aforementioned study (Chang et al., 2003).

Glutamate and Glutamine

Glutamate is the most pervasive excitatory neurotransmitter in the brain. In spectroscopy studies, it is commonly measured along with glutamine, since their MRS signals are difficult to separate. Increased glutamate/glutamine

has been a relatively consistent finding in adult studies of bipolar disorder; this finding is thought to reflect elevated excitatory neurotransmission, and may be relevant to pathophysiological mechanisms in bipolar involving excitotoxicity, or the pathological process by which excessive nerve stimulation leads to nerve damage over time (Yüksel & Ongur, 2010). An early MRS study reported that 10 children aged 6–12 years with bipolar disorder (after a drug washout) showed higher levels of gluatamate/glutamine in the frontal lobes and basal ganglia than10 age-matched healthy control subjects (Castillo et al., 2000).

Myoinositol

Myoinositol is a chemical involved in intracellular signaling and has been implicated in bipolar disorder and in the mechanisms of action for lithium. Patel and colleagues found increased prefrontal cortex concentration of myoinositol in 28 adolescents with bipolar depression in comparison to controls (Patel, Cecil et al., 2008). In a study of 11 children with bipolar disorder and 11 healthy controls, Davanzo and colleagues (2001) reported that patients showed a trend toward greater ACC myoinositol than controls (Davanzo et al., 2001). In another study of children and adolescents with familial bipolar disorder (offspring of one or two parents with bipolar disorder), Cecil and colleagues reported elevated myoinositol levels in the cerebellar vermis in the children aged 8–12 years with bipolar disorder ($n = 9$) in comparison to controls ($n = 10$) (Cecil et al., 2003).

More recently, other approaches using MRS have been explored in pediatric bipolar disorder. In contrast to the studies discussed above which used protron spectroscopy, Sikoglu and colleagues (2013) used phosphorus MRS to assess markers relevant to mitochondrial activity. This study found that although there were no group differences in pH between patients (8 youths with bipolar disorder) and controls ($n = 8$), frontal pH was correlated with age in the bipolar disorder group. Inorganic phosphate levels were lower in the patients, and global phosphocreatine to inorganic phosphate levels was higher in subjects with bipolar disorder compared with the healthy group. These findings represented early evidence for mitochondrial dysfunction in youth with bipolar disorder (Sikoglu et al., 2013) and are in line with a growing body of research in adults implicating dysfunctional mitochondrial functioning and oxidative stress in the neurobiology of bipolar disorder (Andreazza, 2012).

Studies Comparing Pediatric Bipolar Disorder to Other Pediatric Psychiatric Groups

Due in part to the controversy over the diagnosis of bipolar disorder in children, there has been a growing interest in developing biomarkers that could be used clinically to distinguish between psychiatric disorders. A handful of studies have emerged comparing children and adolescents with bipolar disorder to other psychiatric groups, as a first step in the search for neuroimaging-based biomarkers to differentiate psychiatric diagnoses. Frazier and colleagues (2008) used structural MRI to assess children and adolescents aged 6–17 years with either bipolar disorder ($n = 35$) or schizophrenia ($n = 19$) and a healthy group ($n = 29$). They reported that boys with schizophrenia had the smallest left amygdala volumes, and that girls with bipolar disorder had the smallest left hippocampal volumes. Exploratory analyses also suggested larger right nucleus accumbens volumes in bipolar disorder patients compared with controls (Frazier, Hodge et al., 2008). Using MRS, Davanzo and colleagues (2003) measured neurometabolite levels in 10 young patients with bipolar disorder, 10 with intermittent explosive disorder, and 13 normal comparison subjects. They found that the bipolar disorder group showed greater myoinositol levels than both other groups in the ACC, but no significant neurometabolite differences were noted in the occipital cortex (Davanzo, Yue, et al., 2003). Moore, Biederman, Wozniak, and colleagues (2006) used MRS to examine children aged 6 to 13 years with ADHD and no comorbid disorder ($n = 15$), ADHD plus bipolar disorder ($n = 8$), or no psychiatric disorder ($n = 7$). In contrast to the aforementioned studies, this study found that only the ADHD children showed a significant difference from controls: ADHD children showed greater glutamate/glutamine to myoinositol compound ratios than controls, while no differences in brain chemistry were identified between children diagnosed with early onset bipolar disorder and healthy controls (Moore et al., 2006). In summary, the studies examining neuroimaging biomarkers to distinguish youths with bipolar disorder from other psychiatric diagnoses have been few, small in size, and have yet to reveal a consistent pattern of findings. Even when group differences are present, there is often considerable overlap between individuals with different disorders, making it quite difficult to find biomarkers that are exclusively indicative of one illness. Nonetheless, the application of multi-method imaging and cognitive to examine a range of biomarkers in the same sample might

be useful to clarify how potential findings such as reduced hippocampal volume, elevated myoinositol and cognitive impairments might be integrated. Considerable research using larger samples and uniform methods will also be necessary to discover and validate reliable biomarkers for pediatric bipolar disorder that could be translated to a clinical setting.

Potential Precursors of Bipolar Disorder

There is some evidence to suggest that anomalous functioning of the stress system is evident even before the onset of bipolar disorder. Olsavsky et al. (2012) assessed youth (8 to 18 years of age) who were diagnosed with bipolar disorder, youth who were at risk for bipolar disorder (no history of a mood disorder but having a first degree relative with bipolar disorder), and healthy controls in the scanner while they either passively viewed fear or happy faces or while they rated the intensity of these faces. Both the bipolar and the at-risk groups exhibited greater activation of the amygdala while viewing fearful faces than controls (but no differences were found for viewing happy faces). Ladouceur and colleagues (2013) assessed a group of healthy offspring of bipolar parents and found that, relative to healthy controls, bipolar offspring exhibited greater right ventrolateral prefrontal cortex (VLPFC) (BA47) activation in response to positive emotional distracters and reduced VLPFC modulation of the amygdala in response to both the positive and negative emotional distracters. The authors suggest that alterations in the functioning of frontolimbic systems implicated in voluntary emotion regulation may represent neurodevelopmental markers of risk for future onset of bipolar disorder. Roberts, Green, Breakspear, et al. (2013) used MRI to examine young adults (age 18 to 30) who had at least one first-degree relative diagnosed with bipolar disorder within the context of an emotional go, no-go task. The at-risk group showed reduced recruitment of the inferior frontal gyrus during inhibition of emotional stimuli. Many of the at-risk participants were diagnosed with MDD at the time of the scan. Together, these studies indicate that key frontolimbic abnormalities can be identified in at-risk youth, prior to the onset of illness.

In the aforementioned studies that focus on children and adolescents younger than age 18 who are at risk for bipolar disorder, the study design can only provide limited information about whether abnormalities in these youths represent risk or protective mechanisms. Because only a small minority (approximately 10%) of these younger at-risk youth will go on to develop bipolar disorder, it is important to also consider research in which participants are past the age of elevated risk to distinguish if these problems are a precursor to (and therefore a biological marker for) bipolar disorder. Family risk studies that examine neurobiological markers in participants who are past the typical age of disease manifestation are critically important to understanding protective factors. Krüger et al. (2006) assessed transient sad mood in middle-age adults (mean of 38 years) diagnosed with bipolar disorder and their siblings. Using positron emission tomography (PET), they found that all participants showed increases in cerebral blood flow in the dorsal/rostral anterior cingulate cortex and anterior insula, and decreased cerebral blood flow in the orbitofrontal and inferior temporal cortices. Cerebral blood flow in the medial frontal cortex differed across groups, with adults diagnosed with bipolar disorder showing decreased activation while their unaffected sibling showed increased activation of this regulatory brain region during transient sadness. The authors go on to suggest that this sibling response may represent a compensatory effect in youths that are at familial risk for bipolar disorder, which may be a marker of resilience in this group.

Developmental Trajectories

Given the important neurodevelopmental changes that take place across the window of time when bipolar disorder emerges, and the important differences in neurobiology that exist between youth and adult-onset bipolar disorder, an understanding of how and when neural abnormalities first appear and develop over time is greatly needed.

Cross sectional studies comparing adolescents and adults with bipolar disorder have helped to identify neurobiological continuities and discontinuities between the two populations. This line of research may help us understand differences in the manifestation and developmental progression of bipolar disorder over time. Weathers et al. (2012) examined neural circuits mediating motor inhibition under conditions of successful and unsuccessful response inhibition in children ($n = 16$) and adults ($n = 23$) with bipolar disorder, along with healthy children ($n = 21$) and healthy adults ($n = 29$). During successful inhibition, both child and adult bipolar groups showed lower activation of left ventral prefrontal cortex and right nucleus accumbens compared with healthy controls. However, during unsuccessful response inhibition, the anterior cingulate

cortex dysfunction varied developmentally, with lower activation in youths with bipolar disorder than controls, and greater activation in adults with bipolar disorder than controls. This research group later reported results from the sample using a cognitive flexibility task (Weathers et al., 2013). In that study, children with bipolar disorder showed greater activation in frontal, temporal, and parietal activation than controls, whereas adults with bipolar disorder showed hypoactivation in those areas.

Another approach is to study adults with bipolar disorder of the same age but with different onset times (childhood/adolescence vs. adulthood) to better characterize the unique features of early-onset bipolar disorder. Compared with the approach discussed above, this methodology has an advantage in that it does not compare groups of vastly different ages and neural development, which could serve as a confounding factor in the comparison of adult and pediatric bipolar disorder. A recent study found that pediatric-onset bipolar disorder had lower fractional anisotropy (i.e., lower white matter integrity) than those with adult-onset bipolar disorder in the anterior limb of the internal capsule (Lu et al., 2012). Together with findings discussed earlier suggesting that (1) children and adolescents with bipolar disorder may have smaller amygdala volumes than their healthy counterparts, in contrast to adults with bipolar disorder who do not show this finding (Pfeifer et al., 2008); (2) patients with early-onset bipolar disorder show greater numbers of copy number variations in their DNA (Malhotra et al., 2011; Priebe et al., 2011); and (3) patients with early-onset bipolar disorder have higher rates of ADHD (Biederman et al., 2013), these converging cross sectional findings suggest that the neurobiology of bipolar differs according to the developmental time period when it emerges. However, there are still many unknowns with respect to how these neurobiological indices change over time, along the course of illness and during the transition into and through adulthood.

Despite the mounting evidence that pediatric bipolar disorder is associated with abnormal neurobiological development, only two studies have utilized a longitudinal design to examine how the trajectory of brain development may be different for youth who eventually develop bipolar disorder compared with healthy controls and high-risk youth who do not develop bipolar disorder. First, Adleman et al. (2012) examined brain volumes over the course of two years in youth with either narrow phenotype bipolar disorder (using explicit *DSM-IV* criteria, including well-demarcated mood episodes), severe mood dysregulation (SMD; per Leibenluft's definition, described above), or healthy controls. At baseline, both bipolar disorder and SMD groups showed greater volume of dorsolateral prefrontal cortex (DLPFC) and insula. Additionally, the bipolar disorder group showed larger globus pallidus volumes than controls. After two years, the bipolar disorder group, but not the other groups, showed an increased volume of the superior/inferior parietal lobule and the precuneus. The precuneus mediates attention shifting and is involved in episodic memory retrieval and theory of mind, along with being a part of the default mode network (Cavanna & Trimble, 2006). It may be that this increase in the default mode network regions in the bipolar disorder group could underlie a tendency in these patients to have a smaller reduction in the default mode network with increasing task demands (Costafreda et al., 2011). In the second study, Gogtay and colleagues examined longitudinal morphology in a small group of high-risk participants prior to and after converting to bipolar I disorder in adolescence (Gogtay et al., 2007). This study used gray matter density analyses to identify regional differences and changes across time. In adolescents that eventually developed bipolar I disorder, cortical gray matter increased in the left temporal cortex and decreased bilaterally in the anterior cingulate cortex, including the subgenual cingulate cortex. Notably, this pattern was distinct from a pattern that has been identified in childhood-onset schizophrenia.

Treatment Effects

Research examining the effects of psychotropic medications on the brain in pediatric samples is of critical importance. And like the debate over the rapidly increasing numbers of youths being diagnosed with bipolar disorder, there has been an accompanying controversy around the treatment of these children and adolescents with mood-stabilizers and anti-psychotic medications. Although there are some studies examining how existing treatments might impact and potentially restore abnormal circuitry, the location and direction of these changes has varied across studies rendering them somewhat inconclusive. Additionally, variability in treatment response rate suggests that individual characteristics may be important to consider when making treatment decisions. In contrast to the severe paucity of studies documenting change in neural circuitry over time in youth with bipolar disorder, there have been more (but still too few) imaging studies examining how existing treatments might impact and potentially restore abnormal circuitry in this population.

First, there is some early evidence from cross sectional studies that treatment with mood-stabilizing medications

leads to beneficial effects, as indexed by various imaging techniques. Although a longitudinal design is optimal for determining the impact of treatments on the brain, some early studies compared medicated and unmedicated patients to gain some initial clues as to how interventions may affect brain anatomy and function. One such small cross sectional study examined hippocampal volumes in 17 adolescents with bipolar disorder and 12 healthy controls, and reported that among the patients, those who were being treated with lithium had larger hippocampi than those not on lithium (Baykara et al., 2012). This report was consistent with other studies suggesting that lithium has a neuroprotective effect (Machado-Vieira, Manji & Zarate, 2009) and indicates that lithium could promote or facilitate the generation of new neurons in the hippocampus that had previously been hampered by the disease process. Another volumetric study examined subgenual anterior cinculate cortex (sgACC) volumes in 51 children and adolescents with bipolar disorder and 41 healthy controls, and reported that current use of a mood stabilizer was associated with greater sgACC volumes (Baloch et al., 2010). The restoration of sgACC volume would address a well-known abnormality in bipolar disorder (Ongur, Drevets & Price, 1998). Using MRS, Moore and colleagues compared 10 children with bipolar disorder in the manic phase who were not being treated with an antipsychotic medication with eight children with bipolar disorder who were stably treated with the antipsychotic risperidone. Results showed that the untreated group had (1) lower glutamate/glutamine in the ACC; (2) higher severity of manic symptoms; and (3) a negative correlation between clinical and ACC glutamine levels (Moore et al., 2006). Another MRS study of 22 children and adolescents with bipolar disorder (seven unmedicated) and 10 healthy controls that also examined the ACC reported that unmedicated subjects with bipolar disorder had lower glutamine levels than both other groups; no group differences were found with regards to glutamate (Moore et al., 2007). These cross sectional MRS findings provided the basis for hypothesizing that when successful, bipolar treatments may serve to restore abnormal glutamate/glutamine levels in the ACC. However, as we will show, this hypothesis has not been borne out with longitudinal work.

In the first study to longitudinally examine the impact of treatment on neurometabolites in pediatric bipolar disorder, Davanzo and colleagues examined 11 children with bipolar disorder (mean age 11.4 years) and 11 normal controls before and after a 7-day course of lithium using MRS. At baseline, the patients showed a trend toward greater ACC myoinositol than controls, and after treatment, there was a significant reduction in myoinositol and creatinine in the patients, especially among responders (Davanzo et al., 2001). In a later study, however, Patel and colleagues showed myoinositol changes in the opposite direction with lithium in the later phase of treatment: in 28 adolescents with bipolar disorder in the depressed phase, there were no significant changes between baseline to day 7, but myoinositol levels in the right and left dorsolateral prefrontal regions increased between day 7 and day 42 (Patel et al., 2006). Together, these studies preliminarily suggest that lithium treatment could lead to an initial decrease in myoinositol in the ACC followed by an increase in myoinositol in the dorsolateral prefrontal cortex after several weeks of treatment. In a separate publication of their study, Patel and colleagues (2008) reported that medial ventral prefrontal N-acetyl-aspartate (NAA) concentrations decreased over time, with endpoint concentrations significantly lower than baseline concentrations. They did not find NAA concentration changes for left or right ventral lateral prefrontal cortices (Patel et al., 2008). A decrease in NAA with treatment does not reflect a normalization pattern (the majority of MRS studies listed above reported abnormally low NAA in pediatric bipolar disorder). Additional research is needed to determine whether this decrease in NAA with treatment represents a spurious finding, a true mechanism of lithium, or adaptive change in the setting of other changes in the brain with lithium treatment.

In the first longitudinal study to examine the effects of an atypical antipsychotic medication on brain metabolites in pediatric bipolar disorder, DelBello and colleagues (2006) examined hospitalized adolescents with bipolar I disorder ($n = 20$) before, during and after treatment with olanzapine monotherapy. Ten healthy controls were also scanned at the same time intervals but received no treatment. In the first week, manic adolescents had an increase in right lateral ventral prefrontal choline. Remitters showed greater increase in ventral medial prefrontal NAA compared with nonremitters. Baseline medial ventral prefrontal choline was greater in remitters than nonremitters (DelBello et al., 2006). The authors interpreted their findings by suggesting that when olanzapine is successful, the mechanism of action may involve increasing neuronal viability, and that olanzapine-induced increases in choline may lead to alteration in cell membrane metabolism or second messenger pathways that have been implicated in the pathophysiology of bipolar disorder. A more recent study reported the impact of a course of 8 weeks of treatment with quetiapine or placebo on neurometabolites in the ACC in adolescents with bipolar disorder ($n = 26$).

Results indicated that post-treatment, responders had lower myoinositol than responders. However, no metabolites that were measured were noted to have changed significantly as a result of treatment, nor were there any pretreatment neurometabolite measures that predicted treatment response (Chang et al., 2012).

A small-scale treatment study was conducted in which eight adolescents with bipolar disorder (either type I, type II or not otherwise specified) were scanned prior to and following an 8-week trial of the anticonvulsant lamotrigine (Chang et al., 2008). At baseline, amygdala activation in response to negatively emotional stimuli was correlated with severity of depressive symptoms. Participants with greater improvement in depressive symptoms across the 8-week trial had greater reductions in amygdala activation. While this initially appears promising, this pattern has been shown in studies of adults with major depression using PET, in which reduction of amygdala metabolism was correlated with reductions in depression symptoms with antidepressant treatment (Drevets, Bogers, & Raichle, 2002). Therefore, it can be hypothesized that reduced amygdala activation after treatment with lamotrigine, which has an FDA indication for bipolar depression in adults, is a more general measure reflective of recovery from depression as opposed to a direct drug effect.

Finally, Miklowitz and colleagues (in press) evaluated brain changes associated with family-focused therapy in a small group of youth with bipolar disorder ($n = 12$) and evaluated a small group of healthy controls at baseline ($n = 12$). They conducted fMRI during an implicit emotion task at baseline (before therapy) and after 4 months of therapy. At baseline, bipolar youth relative to controls showed hyperactivation of the posterior cingulate cortex and hypoactivation in the dorsolateral prefrontal cortex. Associated with treatment, bipolar youth showed decreased activation of the amygdala and increased activation of the dorsolateral prefrontal cortex. Also, greater increases in dorsolateral prefrontal activation were associated with improvement in manic symptoms.

In summary, emerging research has been conducted using neuroimaging techniques before and after treatment to examine neural mechanisms associated with response to a range of treatments for pediatric bipolar disorder. There is some suggestion from these studies that currently available treatments for bipolar disorder exert measurable changes in the brain, although the location and direction of these changes has varied across studies. Although prechange–postchange tests have not always yielded strong results, analyses examining responders versus nonresponders have been more fruitful, as have some approaches analyzing correlations between treatment response and brain changes. This suggests that some of the early signals being identified may represent mechanisms of response (improvement) rather than simply drug effect. Additional research with larger samples is needed to confirm and extend these findings and to develop reliable biomarkers of treatment response that could be applied in clinical practice.

Summary

Abnormalities in neural circuitry mediating emotion information processing have been found to be implicated in bipolar disorder. As reviewed above, the extant body of neuroimaging research in pediatric bipolar disorder has broadly implicated neural circuitry that has also been implicated in emotion regulation. Across imaging modalities, the findings have suggested large-scale structural changes, multiple functional abnormalities, and even differences in cellular functioning as reflected by neurometabolite abnormalities. This circuitry involves the medial prefrontal cortex and reciprocal limbic connections with the amygdala, hippocampus, ventral striatum, hypothalamus, and brain stem (Ongur & Price, 2000; Savitz & Drevets, 2009). Emerging evidence suggests that the structure, activation, and chemistry of these regions are frequently altered in youths with bipolar disorder, and that the pattern of abnormalities is not always the same in youths as those seen in adults with bipolar disorder. Additional research is needed that uses multiple methods to integrate the different neurobiological measures and to provide a more over-arching model for the disorder. Research examining how developmental trajectories in youth with bipolar disorder may be abnormal is still in its infancy but shows promise for shedding light on the neurodevelopmental basis for the illness. The extant work examining treatment effects on neurobiological indices provides the foundation for the future generation of translational research integrating neuroimaging with clinical trials. The next steps in this research will require larger and more homogenous samples to confirm initial findings, and should test novel treatments that might more successfully restore healthy developmental trajectories in youth with bipolar disorder.

TRANSLATIONAL IMPLICATIONS

Translational research refers to the application of knowledge gained by basic science research to clinical applications such as the characterization, treatment, and

prevention of pathology. In this section, we identify major themes that will continue to guide future research and discuss some translational implications by once again returning to the core principles of developmental psychopathology. Addressing the core features of the illness by developing hypothesis-driven early interventions and preventive strategies are high-priority goals for the field (Insel, 2009). It is imperative to continue to conduct foundational research to enhance our understanding of how psychopathology unfolds across development (Lee et al, 2014).

Better Classification Will Lead to Better Prevention and Intervention Strategies

The traditional classifications of mental illnesses have a number of limitations for understanding and treating bipolar disorder. Because the *DSM* is still the primary framework for the diagnosis of bipolar disorder in youth and adults, research to identify the prevalence, course, precursors and treatment of the disorder almost exclusively relies on these categorical approaches to design studies. The current categorical criteria often lump together patients with very different collections of symptoms (and likely very different etiologies for their illness). As McNally (2012) has pointed out, two individuals can be diagnosed with the same disorder without sharing a single symptom. By fostering heterogeneous definitions of disorders, it is possible that the *DSM* may now impede research on mental illnesses, rather than assisting it (Cuthbert & Kozak, 2013; Uher, 2013). Many agree that a new approach to classification of mental illness is needed.

The hope is that some of the most serious flaws associated with the categorical approach can better be addressed by employing empirically derived dimensional models of developmental psychopathology. Recent research using dimensional approaches have already started to shape ways the macrostructure of psychopathology is being viewed by the psychiatric community (e.g., Krueger & Markon, 2006). Consideration of symptom aggregation patterns may also help to address some of our current challenges in determining whether children with broadly defined pediatric bipolar disorder (e.g., DMDD) or common patterns of comorbidities (e.g., comorbid pediatric bipolar disorder-ADHD) should be treated the same as children with the narrowly defined bipolar I and II disorders (Biederman et al., 2013). Clarifying the etiological relationship of these disorders has significant clinical implications. For example, it is possible that under these more varied conditions, the standard treatments for bipolar disorder may not be effective. Determining which sets of symptoms respond to specific treatments could help prevent young children from being prescribed medications that would have side effects and not actually ameliorate their condition. Personalized intervention strategies may prove to be effective in altering the course of bipolar disorder by matching specific interventions to specific problem profiles rather than adopting more traditional one-size-fits-all approaches. Additionally, although there continues to be some debate about the progressive nature of bipolar disorder, clinical staging models may also guide intervention selection. For example, relatively benign prevention and intervention strategies (e.g., CBT, social rhythm therapies) could be deployed when developmental perturbations are first detected, leaving more advanced and virulent forms of the illness to be treated with psychopharmacological interventions which carry more significant potential side effects.

Better Understanding of the Etiology and Neurobiology Will Lead to More Effective Preventive and Intervention Strategies

Ideally, empirically based diagnostic criteria will clarify the etiology of specific symptoms, facilitating the development of more effective ways to intervene. While the atheoretical approach to classification was initially a reaction to outdated etiological theories that had dominated earlier versions of the DSM, researchers are increasingly recognizing that effective treatment of psychopathology will require etiologically valid diagnoses. Some of the advances will likely be informed by a better understanding of the neurobiological and genetic underpinnings of the illness. For example, if researchers determine that pediatric-onset bipolar disorder is continuous with adult-onset bipolar disorder, it could indicate that bipolar medications typically used with adults could be effective among youth.

Efforts to develop classification systems that go beyond a complete reliance on self-reports and instead attempt to connect core disruptions in behavior with the underlying neurocircuitry are a priority for the field. These efforts will eventually help develop a neuroscience-based definition of bipolar disorder that is informed by critical contextual factors. This general approach has been promoted by RDoC and is sometimes referred to as a psychoneurometric approach (Morris & Cuthbert, 2012; Moser et al., 2014; Patrick, Durbin & Moser, 2012); one that reconceptualizes clinical disorders in terms of dispositional constructs and their neurobiological underpinnings. Indeed, this approach is leading to answers about how different interventions reduce the symptoms of mental illnesses at a

neurobiological level. For example, there is now evidence that offspring of parents who are lithium responders show a different profile of symptoms from offspring of parents who are lithium nonresponders (Duffy et al., 2002). It is hypothesized that these subgroups may show varied responses to intervention depending on their underlying neurobiological features. Recent research has also been conducted using neuroimaging techniques before and after treatment to examine neural mechanisms associated with response to a range of treatments for pediatric bipolar disorder. Although pharmacological and psychological interventions show some efficacy in the treatment of pediatric bipolar disorder, remission rates are highly variable. Given that any one risk or protective factor is not likely to lead to development of interventions, the use of data aggregation methods across systems, or big data approaches as it is sometimes called, might be an important tool for characterizing the etiology of bipolar disorder and suggesting ways to intervene (McIntyre et al., 2014). It is possible that by examining core symptoms, behaviors, or underlying neurobiological markers of bipolar disorder, progress can be made in identifying more precise predictors of treatment responses, along with identifying neurobiological targets for intervention.

Longitudinal research is needed to understand the natural history of the illness, as "a deficit occurring early in development can give rise to a cascade of more complex deficits as different brain regions mature and interact over time … with environmental events and other contextual factors" (Casey, Oliveri, & Insel, 2014, p. 351). Special issues of *Development and Psychopathology* (edited by Masten & Cicchetti, 2010) have focused on developmental cascades, which are central to developmental psychopathology and are crucial to understanding how cognitive and neurobiological deficits can change throughout development. As part of this special issue, Klimes-Dougan et al. (2010) addressed developmental trajectories in children at risk for bipolar disorder. They demonstrated that self-regulation deficits identified in offspring of bipolar and unipolar depressed parents show very distinct developmental paths across childhood and into adolescence, with offspring of unipolar parents cascading into internalizing pathology and offspring of bipolar parents tending to cascade into thought problems. Information about the trajectory of the illness will inform prevention and intervention science, by identifying typical developmental periods which intervention might be most suitably targeted as well as bringing attention to the importance of developmentally sensitive intervention strategies.

The most effective way to study the developmental progression of psychopathology is through multiple levels of analysis. As some researchers have pointed out, brain development occurs across different systems in synergistic and antagonist manners: "Early in development, brain circuits across different regions interact dynamically. The cumulative consequences of these interactions among developing systems alter the course of development" (Casey et al., 2014, p. 351). Capturing this dynamic interaction requires research from multiple perspectives. Developmental psychopathology frameworks are at the forefront of this challenge, with special issues of *Developmental and Psychopathology* focusing on multiple levels of analysis relevant to externalizing (edited by Burnette & Cicchtti, 2012) and internalizing (edited by Cicchetti & Natsuaki, in press) pathology.

Better Understanding of Risk and Protection Will Lead to More Effective Preventive and Intervention Strategies

Protective factors should be more fully examined to develop more effective prevention and intervention strategies. Towards this end, it is important to keep in mind that some risk and protective factors are common to most forms of psychopathology. For example, there is now evidence that parenting dynamics can affect the onset of bipolar disorder (Meyer et al., 2006) and relapse after recovery from mania in youth (Geller, Tillman, Craney & Bolhofner, 2004). Additionally, the structure provided by parents in childhood, predicts cortisol reactivity among offspring of bipolar parents in adolescence (Ellenbogen, Hodgins, Linnen & Ostiguy, 2011). Together this evidence suggests that etiological models should account for familial and environmental factors, which may be a potential target for intervention (as in family-focused therapy and Interpersonal and Social Rhythm Therapy). It is also important to be aware that risk factors for some conditions can be protective factors for other conditions and should not be viewed as being intrinsically detrimental or beneficial. For example, positive affect, optimism, and goal-directed behavior are often identified as protective factors for mental illness (Vahia, Chattillion, Kavirajan & Depp, 2011). Fredrickson and Branigan (2001) have explored how positive affect may be an evolutionarily derived characteristic because it increased the stability of communities. They suggest that our ancestors likely built personal resources, including resources for survival, during safe and satiated moments, by playing and exploring when positive affect predominated. However, positive affect, optimism, and goal-directed behavior have also been

found to be characteristic of bipolar disorder or prodromes of the disorder (Johnson, 2005b). Some research has also linked bipolar disorders to profile of other assets that are rarely systematically associated with mental illness, including heightened creativity, academic achievement, and intellectual performance (Johnson, 2005b; Murray & Johnson, 2010). Accordingly, a number of considerations will need to be made to incorporate this knowledge into prevention and intervention strategies, like recognizing that rapidly increasing positive affect in an individual suffering from bipolar depression may actually stimulate a manic episode, rather than helping the individual return to a euthymic state.

In summary, translational applications for developmental psychopathology principles will be important for prevention and intervention. Success in this field is likely to draw from advances in phenomenological, etiological, and neurobiological research on bipolar disorder in youth. Longitudinal research and intervention studies will be critical for continuing to address many of the gaps in our current understanding of this neurodevelopmental disorder. We are still learning how the normal brain develops and which neural features are associated with atypical brain development and a poor prognosis (e.g., Fristad & Algorta, 2013). It is highly likely that some of the current challenges in effectively treating bipolar spectrum disorders in youth would be ameliorated by more fully understanding the development of the illness.

SUMMARY AND CONCLUSION

Developmental psychopathology is a conceptual approach that addresses development and variation in development, with a particular emphasis on mechanisms and processes associated with adaptation and risk (Cicchetti & Cohen, 2006; Rutter, 2013). In the last 25 years, we have seen significant advances in our knowledge of bipolar disorder in youth (Fristad & Algorta, 2013), including the publication of major reviews of progress in understanding bipolar disorder from a developmental psychopathology perspective (e.g., Miklowitz & Cicchetti, 2010). This chapter strove to continue these efforts by summarizing progress in three of the domains in which developmental psychopathology has most powerfully shaped our understanding of the risk and protective factors for bipolar disorder: phenomenology, etiology, and neurobiology. Innovative progress is also expected in these three domains in the future.

Beginning with a historical review of the diagnosis of bipolar disorder, we have described some of the major changes to the conceptualization and categorization of the illness. The current controversy over the diagnosis of pediatric bipolar disorder has drawn attention to some major limitations facing psychiatry and clinical psychology, and has prompted a reconceptualization of the basic assumptions guiding research on bipolar disorder. For much of the twentieth century, researchers largely ignored the possibility that bipolar disorder could begin in childhood and adolescence. Clinical and epidemiological research has provided convincing evidence that bipolar disorder is commonly evident prior to adulthood, spawning research in this topic. The often heated controversies about appropriate criteria for bipolar disorder in youth have begun to dissipate with researchers now acknowledging the value of specifying the approach for characterizing bipolar disorder, with some groups focusing on narrow definitions and other groups focusing on broad definitions. Different definitions may be advantageous for answering different research questions (e.g., narrow definitions may be more consistent with adult pathology). Also, clarifications have been made to characterizing the onset and course of bipolar disorder. The age-of-onset may be the crucial factor determining the severity and type of bipolar disorder that individuals eventually experience.

Beyond the traditional, categorical diagnostic approaches used to characterize psychopathology, empirical approaches using phenotypic dimensions are being increasingly explored. Empirical models have been important in characterizing the macro-structure of more common forms of psychopathology in children and adults. Empirical models are also showing that bipolar disorder has less in common with unipolar depression than was once believed. Rather, these models indicate that bipolar disorder is closely aligned with thought disorders like schizophrenia and cluster A personality disorders, as well as broader indexes of internalizing and externalizing psychopathology. These more recent approaches to classification complement the views inherent to developmental psychology, in which risks for mental disorders and mental disorders themselves are considered largely dimensional phenomena (Rutter, 2013). This work on the phenotypic classification of symptoms, syndromes, and disorders is foundational to advancing the developmental study of pediatric bipolar disorder and continues to be pivotal in facing the challenge of how best to treat youth suffering from this illness.

In the first section of this chapter we also discussed definitions of psychopathology that focus on behavior and underlying neurobiological substrates, rather than relying exclusively on phenotypes based largely on subjective

experiences and self-reports. While these models are still imperfect and incomplete, the Research Domain Criteria (RDoC) initiative and the growing prominence of work that serves to identify biomarkers and endophenotypes reflect a major shift in the field toward another type of empirically based definitions of mental illness. These efforts should also help researchers eliminate the heterogeneity that has slowed and frustrated research on bipolar disorder, particularly pediatric bipolar disorder. Ultimately, this research intends to establish more valid and reliable characterizations of symptoms, syndromes, and disorders, which should allow clinicians to treat the true causes of an illness. Progress in understanding the causes and underlying neurobiological mechanisms of bipolar disorder in children and adolescence will need to incorporate developmentally appropriate theories and assessment strategies.

The second section of this chapter focused on etiological theories of bipolar disorder. Although the specific causes of bipolar disorder are still unknown, our current etiological models of mental illness have progressed sufficiently to incorporate greater complexity and to embrace the myriad of interactions between biology, the environment, and development. We started our discussion of etiology by considering the important—though somewhat limited—research on environmental contributions to bipolar disorder. While there is strong evidence that biological contributions to bipolar disorder are important, nongenetic factors are responsible for up to 40% of illness susceptibility. That is, environmental stresses and hazards dramatically affect the risk, onset, and course of bipolar disorder in a number of different ways. Life stress, particularly when experienced in early childhood, is thought to have a deleterious impact on adaptation. The results support this more general pattern of risk shared by many stress regulatory disorders (e.g., depression and schizophrenia), showing an increased risk for bipolar disorder in those who experience early life stress. By contrast, the evidence for links between early hazards and susceptibility to bipolar disorder (e.g., perinatal insults and complications) is less clear. The model proposed by Murray and colleagues (2004) contends that patients with schizophrenia, but not those with bipolar disorder, exhibit critical developmental differences related to such early insults. It is possible that hazards introduced later in development have a similar impact on the ongoing development of the neurobiological system (e.g., marijuana use in adolescence) and may negatively impact the onset and course of bipolar disorder, similar to the way they increase risk for schizophrenia. Although to the specific role of environmental stresses and hazards still remains speculative and requires further investigation, recent findings point to the potential importance of examining developmentally sensitive environmental risk factors for bipolar disorder. Models that more fully incorporate environmental contributions to bipolar disorder and consider the biological embedding of experiences represent an important area of continued inquiry.

The second half of the etiology section reviewed the genetics of bipolar disorder. Genetics research is beginning to contribute to models that illustrate how genes are probabilistic and not deterministic causal factors for bipolar disorder, and how the environment can influence genetic risk for an illness. Recent behavioral and molecular genetics research has not yet adequately investigated the genetics of pediatric bipolar disorder, but it has started to make significant progress in mapping the genetic etiology of adult mental illnesses. Behavioral genetics studies have fairly consistently shown that between 60% and 90% of susceptibility to bipolar disorder is caused by additive genetic factors. While bipolar disorders were once thought to be caused by a few bipolar genes, evidence from extensive family and twin studies—along with the failure of gene-linkage research—has definitively shown that this is not the case. Instead, genome-wide association studies (GWAS) and statistical analysis like genome-wide complex trait analysis (GCTA) are showing that bipolar disorder—like most complex psychiatric illnesses—is most likely to be caused by thousands of common single-nucleotide polymorphisms (SNPs) with very small effects and by a smaller number of rare variants (both SNPs and structural variants) with fairly large effects. This pattern of susceptibility likely explains why current GWA studies with relatively small numbers of participants and low-resolution microassays have only been able to identify a few causal genetic variants (the problem of missing heritability). Nonetheless, existing genetics research has advanced our understanding of commonalities and differences between what we currently consider different classes of psychiatric disorders (e.g., bipolar disorder shares a large portion of its genetic composition with schizophrenia). Finally, although they remain speculative and less understood, several promising approaches are being considered for understanding the way that genetic risk for bipolar disorder can be affected by environmental factors, including epigenetics and specific gene–environment interactions. Genetics research continues to advance very quickly, and while it is likely that the genetic architecture of bipolar disorder will be complex and multifaceted, we remain cautiously optimistic this progress will eventually translate into better methods for

characterizing bipolar disorder and will aid in enhancing intervention options.

In the third section of this chapter, we turned our attention to the structure and function of the brain in youth diagnosed with bipolar disorder, another rapidly growing field of research. We briefly reviewed neurocognitive studies and then more comprehensively reviewed neuroimaging studies on pediatric bipolar disorder across a wide range of modalities including volumetric analysis, task and resting-state functional MRI, diffusion tensor imaging, and spectroscopy. These studies have documented substantial differences in the neuroanatomy and neural functioning of youths with bipolar disorder in comparison to healthy controls, youths with other psychiatric disorders, and even adults with bipolar disorder. Some of the major differences involve brain regions implicated in emotional regulation, such as limbic regions (e.g., amygdala, hippocampus, and cingulate) and cortical regions such as the dorsolateral prefrontal cortex. Some core documented differences are that bipolar youth show smaller amygdala volumes; hyperactivation of limbic regions; less white matter integrity in the corpus callosum, internal capsule, and cingulum (though the specific areas of difference has varied between studies); and abnormalities in some neurometabolites (e.g., N-acetyl-aspartate, choline-containing compounds, glutamate/glutamine, and myoinositol) that reflect possible decrements in the status of cellular health and function in the brain. These studies, while still somewhat preliminary due to small and heterogeneous sample sizes, support theories that bipolar disorder involves neurodevelopmental abnormalities (abnormal dendritic arborization and neuropil), elevated excitatory neurotransmission and excitotoxicity, and abnormal intercellular signaling. While the studies searching for neuroanatomical biomarkers for the disorder that can reliably distinguish it from other disorders have generally been few, small in size, and inconsistent, future use of multiple imaging modalities, larger samples, and more uniform methods could help identify potential biomarkers. Neuroimaging studies have also been used to determine potential precursors to bipolar disorder and its developmental trajectory in youths. These studies support the notion that there are neuroanatomical precursors to the disorder, including key frontolimbic abnormalities. They have also shown that the neurobiology of the bipolar disorder varies according to the developmental period in which it first emerges (e.g., childhood or adulthood). Finally, treatment research has shown preliminary evidence that anomalous brain functioning can be normalized with medication and points to some possibilities for using neuroimaging to predict response to treatments. We believe this line of research has great potential for continuing to help characterize the neurobiological underpinnings of bipolar disorder, and to shape our ideas about susceptibility to the illness and its course and outcomes.

In closing, this is an extremely exciting time for the developmental study of bipolar disorder. The past two decades have witnessed technological innovations and methodological advances that have laid the foundation for current research. Empirical models of mental illness are combining with new information from genetics, neuroimaging, and longitudinal studies to paint a more accurate and complex picture of bipolar disorder. We are finally starting to understand how the disorder progresses and the role that development and environment play in the onset, course, and prognosis of the illness. While years of research will be required to more fully elucidate the etiology, along with risk and protective factors, the direction of research is becoming clearer. New frontiers in biological psychopathology research on bipolar disorder will include longitudinal designs examining risk and protective factors and continued examination of brain-behavior relationships using multiple levels of analysis across a range of participants (e.g., individuals not fitting traditionally defined psychiatric categories). Much of this research is still in its infancy, and it may be another decade before many of the fundamental questions about pediatric bipolar disorder are answered. What is important to recognize is that researchers are beginning to question some of the long-standing assumptions about bipolar disorder, and are searching for empirical answers using longitudinal, multidisciplinary research approaches. Prevention and intervention research must draw from the advances yielded by phenomenological, etiological, and neurobiological research to help relieve the suffering of those diagnosed with bipolar disorder.

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CHAPTER 21

Childhood Schizophrenia

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INTRODUCTION

Schizophrenia is regarded as a developmental disorder because it involves abnormal function of multiple brain regions and neural circuits that become apparent during development (Weinberger, 1987). Thus, most individuals present with symptoms of schizophrenia during late adolescence or young adulthood. Childhood onset of the disorder is considered rare, associated with more severe positive and negative psychotic symptoms (Table 21.1), and with worse prognosis than the later onset disorder (Frazier et al., 2007). However, well-designed epidemiological outcome studies that include a large representative number of subjects with different ages of onset and illness severity are needed to confirm this assumption.

This chapter first introduces the reader to the need for a developmental approach to diagnose schizophrenia in children, the related clinical and research implications of the challenges involved in making this diagnosis, and the differential diagnosis. It then describes risk factors and premorbid features related to development of the disorder. The next section reviews the impaired cognition, social cognition, and self-disturbance that occur during the acute and chronic phases of the illness.

A detailed review of structural imaging findings sheds some light on the developmental mechanisms underlying the multiple areas of functioning involved in this disorder and their associated symptoms. After briefly reviewing the functional imaging and genetic findings in early-onset

[1]Color versions of Figures 21.1–21.9 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

TABLE 21.1 Positive and Negative Psychotic Symptoms

Positive symptoms
Hallucinations
Delusions
Loose associations
Illogical thinking
Negative symptoms
Affective flattening (lack of facial expression)
Anhedonia (lack of enjoyment)
Alogia (lack of motivation)
Avolition (lack of motivation)

schizophrenia, the chapter describes the treatment and course of the disorder.

Since schizophrenia is a neurodevelopmental disorder, it should serve as a model for the application of Cicchetti and colleagues (Cicchetti, 2006; Cicchetti & Toth, 2009) five developmental psychopathology principles: (1) examination of processes involved in the interaction between adaptive and maladaptive development over the lifetime course and factors involved in resilience; (2) a multiple level analysis that incorporates an interdisciplinary perspective; (3) prevention and intervention initiatives based on theory and research of biological and psychological developmental processes; (4) incorporation of cultural contexts into study designs and treatment initiatives; and (5) translational research.

As will become evident in the research reviewed in the different sections of this chapter, most of the research on child and adolescent onset schizophrenia has not applied these five principles. In addition, there is a dearth of knowledge about the variables that contribute to resilience to childhood and adolescent onset of schizophrenia, the course of the early-onset disease, and its long-term outcome. To fill this gap, in its different sections the chapter incorporates findings of studies on risk factors for adult schizophrenia and of studies on the nonpsychotic relatives and individuals at clinical risk for schizophrenia. The chapter concludes with suggestions for possible future research directions that incorporate the five developmental psychopathology principles.

DIAGNOSIS

The Need for a Developmental Approach

The primary symptoms of schizophrenia, hallucinations, delusions, and formal thought disorder, represent abnormalities of skills, including cognition, language, reality testing, judgment, and organization of thoughts, that develop during childhood and adolescence. Hallucinations (sensory percepts in the absence of an external sensory stimulus) involve impaired reality testing and ability to differentiate between internal and external perception of auditory, visual, tactile, olfactory, or gustatory stimuli. Delusions, pervasive erroneous beliefs despite evidence to the contrary, also represent impaired reality testing and judgment.

The clinical term, formal thought disorder, denotes poor use of language to formulate, organize, and express thoughts so that the listener can make sense of the child's speech (the meaning of each sentence, the ongoing topic of conversation, logical sequence of expressed thoughts), as well as who and what the child is referring to across sentences. It also reflects impaired online monitoring and self-initiated repair of how coherently the child expresses thoughts.

Since the skills involved in these symptoms develop during middle childhood and mature in early adolescence, the manifestations of hallucinations, delusions, and formal thought disorder might differ in children of different ages. Additional *DSM-IV-TR* (APA, 2000) symptoms of schizophrenia, grossly disorganized or catatonic behavior and negative symptoms, also pose diagnostic challenges. Unlike catatonic behavior (which is rarely found in youth under age 15), these symptoms can also occur in children with and without psychopathology.

The Challenges Involved in Applying a Developmental Approach

There are four main reasons why pediatric professionals are challenged when they need to rule in or out a diagnosis of schizophrenia during middle and late childhood. First, they receive inadequate or sparse training on age-related changes in cognition, language, reality testing, and judgment. Second they are infrequently exposed to schizophrenia in children during their medical, psychological, social work, or other mental health training. Third, they sometimes mislabel children's out-of-control or bizarre behavior as disorganized and psychotic. Fourth, they might also feel ill equipped to differentiate normal developmental phenomena, such as imaginary friends and a vivid creative imagination, from both hallucinations and delusions.

A lack of training on how normal and deviant development of children's basic and higher-level discourse language skills present is an additional important obstacle. More specifically, a child professional might have difficulty understanding what a child is talking about because the child has formal thought disorder, a language disorder, intellectual disability, or severe anxiety. The term thought disorder has also been somewhat loosely used as a

synonym of schizophrenia. As such, its connotation varies across users from the impaired thought content found in delusions to the disorganized communication of thoughts found in formal thought disorder.

The challenges emanating from lack of training and exposure and inaccurate use of terms, such as thought disorder are further complicated by the difficulty child mental health-care professionals have obtaining information about psychotic symptoms from children. Most importantly, children resist talking about their psychotic symptoms. They are scared both because they perceive their hallucinatory experiences as unusual and the content of their hallucinations might be threatening (e.g., a voice threatens to kill the child). Although children try to seek comfort or protection by telling their parents about these experiences, parents often respond by telling their children that they are just imagining things. Aware that these experiences are not ordinary, they then conclude that their parents think that they are crazy or at best do not understand what they are experiencing. As a result, they refrain from mentioning recurring hallucinations to their parents and to other adults.

Children who also have magical thinking (another normal developmental phenomenon in middle childhood) might be scared that if they talk about their hallucinations, they will come true. For example, if a voice commands a child to kill his sibling, the child might be scared that talking about this act is tantamount to actually doing it.

Parents or teachers might misinterpret a child's anxiety as disorganized behavior. Moreover, because of their poor insight, children with schizophrenia are poor informants about this symptom. Confirmation of disorganized behavior, therefore, warrants direct observation by an experienced child clinician.

Taken together, these challenges highlight the importance of providing child mental health professionals with developmental guidelines on how to reliably assess symptoms of schizophrenia in children of different ages. This is particularly important because young children are usually the best informants about their psychotic symptoms, disorganized behavior, and what appear to be negative symptoms. The wide range of psychiatric disorders included in the differential diagnosis of childhood schizophrenia described below underscore the need for child mental health professionals to include these skills in their professional toolbox. Due to space limitations, interested readers can find more details on techniques to obtain information from young children on psychotic symptoms and a wide range of behaviors and emotions in Caplan and Bursch (Caplan & Bursch, 2012).

Developmental Guidelines for the Assessment of Psychotic Symptoms

Hallucinations

79%–100% of children and adolescents with schizophrenia have auditory hallucinations, 30.3–78.9% have visual hallucinations, one third have olfactory hallucinations, and less than one fourth have tactile and gustatory hallucinations (McKenna et al., 1994; Russell, Bott, & Sammons, 1989). Auditory hallucinations are commanding, conversing, persecuting, and religious (McKenna et al., 1994; Russell et al., 1989).

As previously mentioned, children typically do not voluntarily tell mental health professionals that they have hallucinations. But they do respond to sensitive developmentally based questions about these experiences. A nonthreatening open-ended question, such as, Does your imagination ever play tricks on you? helps introduce the topic. If the child answers in the affirmative, one should proceed to ask, What tricks? The child might warily answer with a word, such as *noises*, *at night*, *a dream*, or *scary*.

Additional probing questions—What kind of a noise? What does the noise sound like? Who makes the noise? Is it a noise or a voice? What does it say?—help determine the form and content. Once the child responds to questions on the details of the experience (e.g., Is it one or more than one voice? Whose voice is it? What does the voice say? In what language does the voice speak?), one should ascertain if it is associated with subjective distress (How does that make you feel when you hear. . . .?). To determine if the child has poor reality testing, one should find out if the child tries to make it stop and how convinced the child feels about it being a real experience that does not go away.

Similar questions help inquire about visual, tactile, olfactory, and gustatory experiences. It is important to avoid using questions such as, Do you hear voices *that no one else hears*? or Do you see things *that no one else sees*? Since these questions make children feel that the interviewer is suggesting they are 'crazy' or 'weird,' they typically deny these experiences.

To help children talk about these difficult topics, professionals should use concrete action-based language rather than the abstract and vague language used in the following example: Do you have unusual (strange, weird) experiences like seeing things? The connotation of being crazy in the words, unusual, strange, and weird, might make children resistant to talk about their hallucinations.

Hallucinations are rare before age seven. Therefore, reports of hallucinations in children under 7 might represent mislabeling or misinterpretation of behaviors. This

concern is particularly warranted in intellectually disabled or language delayed children. Examples include the concern that a child covering his ears with or without a fearful response or agitated behavior is having an auditory hallucination or that a child looking at something with a fixed look while laughing, mumbling, or acting fearfully might be experiencing a visual hallucination. Most importantly, one can make a reliable and valid assessment of hallucinations only in a child who is able to verbalize the phenomenon.

Hallucinations also need to be differentiated from normal developmental phenomena. Imaginary friends are invisible or personified objects with whom children under age 7 have a sustained form of play, pretence, daily routine, and even arguments (see review in Trionfi & Reese, 2009). In contrast to children with schizophrenia, these children are sociable and have a high level of language skill and good reality testing (Trionfi & Reese, 2009).

It is also necessary to determine if children's fears are age-appropriate or reflect the child's living conditions before concluding that they represent hallucinatory experiences. For example, a child who lives in a neighborhood with frequent drive-by shootings reports hearing gunshots every night when trying to fall asleep. Vivid nightmares might appear real and cause fear when children first wake up. If, however, the child feels as if the dream experience continues during the day, the possibility of a hallucinatory experience needs to be ruled out.

While falling asleep or if they wake up during the night, children might also experience visual illusions (e.g., a pile of clothes on a chair might look like a monster). These misinterpretations of visual stimuli are differentiated from hallucinations by the child's good reality testing for the imaginary quality of the experience when awake in the morning.

Delusions

Delusions often have bizarre content in schizophrenia, and can be persecutory, referential (refer someone's action to one-self), controlling, somatic, religious, self-accusatory (delusions of guilt), and nihilistic (McKenna et al., 1994; Russell et al., 1989). Due to the abstract nature of the concept of delusions, in contrast to hallucinations, no single question is suitable to tap into the delusional process in young children. Clinicians can access information about children's delusions using concrete questions (Table 21.2).

Like hallucinations, delusions are rare in children under age seven, and should be differentiated from normal developmental phenomena, such as fantasies and magical thinking (thoughts and wishes are equated to actions). If a child is cognizant of the imaginary or wishful thinking quality of these thoughts, they do not represent a delusion. Morbid fantasies (repeated elaborate thoughts involving aggression) might be precursors of delusions if they are pervasive and if the child will act on the basis of these thoughts. Given the high level of violence in the media and children's computer games, it is important to differentiate media or game induced recurrent thoughts about violence from delusions.

For example, a child repeatedly thinks about and plans how to kill, blow up, or maim others despite the possible consequences, and says that this will make him very happy. When asked what will happen if he carries out the plan, he responds that he does not care as long as the people are dead, blown up, or badly hurt. This child's pervasive aggressive thoughts, willingness to act on his thoughts, and poor reality testing suggest that they are precursors to delusions.

TABLE 21.2 Questions on Delusions for Children

Delusion Type	Questions
Message	Do people on TV, YouTube, or the Internet say things only for you? What do they say?
Persecution	Are there people who do bad or mean things to you or your family? What do they do?
Reference	When you walk in the street (cross the play ground at school), do kids look at you and talk about you? What do they say?
Somatic	When you look at yourself in the mirror, is there any part of you that looks strange or different? How about inside your body, is everything in there okay?
Thought broadcasting	Do people on TV, YouTube, or the Internet talk about what you are thinking?
Thought insertion	Can people put thoughts into your head and make you think what they want you to think?
Thought withdrawal	Can they take thoughts out of your head and not let you think what you want to think?
Thought control	Do people know what you are thinking? Do you know what other people are thinking?
Motor control	Do you sometimes feel like someone else, not you, is in your body and makes it work?
Guilt	If you do something wrong or bad, do you forget about it or keep on thinking about it? If something bad happens to someone you know, and you had nothing to do with it, do you feel you made that happen?
Nihilism	Do you sometimes worry that the world is going to end?
Grandiosity	Do you have special powers? What special powers? What things can you do that no one else can do? Like what?

TABLE 21.3 Definition and Examples of Thought Disorder

Thought Disorder	Definition	Example
Formal Thought Disorder		
Illogical thinking	Inappropriate or inadequate reasoning or contradiction	I left my hat in her room *because her name is Mary*.
Loose association	Unpredicted topic change to an unrelated topic	I: Why's that not Tim? S: *I call my mom sweetie*.
Cohesion		
Conjunctions	Ties together contiguous clauses (sentences)	The witch gets burned *and* that's the end of the story.
Referential cohesion	Pronoun, demonstrative, definite article, or comparative referring to person/object in the preceding spoken text	A boy called *Peter* saw a ghost. He was scared.
Unclear reference	Pronoun, demonstrative, definite article, or comparative referring to person/object unmentioned in prior text	I went and looked at *the guy* to see what *they* did.
Ambiguous reference	Referent that can apply to more than one person or object	*Her mother* made a costume and *she* was happy.
Exophora	Reference to immediate environment during conversation	I: Did you like that story? S: *Open this toy*.
Lexical cohesion	Ties between ideas by word repetition, synonym, antonym	The kids were *bad*. Tim was bad too.
Repair of the Organization of Thoughts		
Repetition	Clarifies what was said by repeating word(s)	'Cause he wants . . . '*cause he wants* to play with him.
Postponement	Adds background information to clarify referent	And she knew *when she found the kitten* she knew that was what was making the girl happier.
False starts	Starts, but does not complete an idea	*And um I don't* . . . Manniken said but I want to play.
Fillers	Word(s) that fill pauses without changing the meaning	*Well, like,* I don't know, it's just scary.
Revision of Linguistic Elements		
Referential	Clarifies the referent	She would have *Anne would have* to take care of her.
Word choice	Modifies word choice	Play with him and make *give him* some wishes.
Syntactic	Corrects syntactic error	The picture you're drawing *you drew* looks funny.

Disorganized Speech or Formal Thought Disorder

DSM-IV TR signs of formal thought disorder include illogical thinking and loose associations. In contrast to delusions, formal thought disorder involves the form rather than the content of children's communication, and is best ascertained by listening to a child's speech. Table 21.3 presents the thought disorder signs and examples found in children with schizophrenia.

To evaluate formal thought disorder (Caplan, Guthrie, Komo, Tang, & Asarnow, 2000), one should obtain speech samples of adequate length from children. But, young children do not spontaneously talk at length (i.e., in paragraphs) about a topic. Children in this age group need an adult's help to induce them to speak in mini-paragraphs of 1–3 utterances through what or how action-based concrete questions, described in detail in (Caplan & Bursch, 2012).

For example, in response to the question, What do you like to do when you come home from school? a child might answer, Watch TV. To get the child to talk more about this, one can ask, What TV shows are your favorite? What do you like about . . . show? I have never seen . . . show. What happens in the story? What is the best part of the story? What don't you like about the story?

Alternatively, in response to the initial question, a child might answer, I have a snack and watch TV (2 utterances). A child with loose associations will unpredictably change the topic of conversation without preparing the listener for the topic changes and respond, My sister is in fourth grade. A child with illogical thinking might answer to the same question, I nap because I have a lot of energy. The causal phrase *because I have a lot of energy* contradicts the act of napping and is illogical.

Younger children with schizophrenia have significantly more thought disorder than older children with this disorder (Caplan et al., 2000). This finding reflects the previously described protracted course of language development, particularly of higher-level discourse skills involved in the organization, processing, and abstract contextual aspects of discourse (inferences, metaphors, jokes, sarcasm). Thus, onset of schizophrenia during ongoing maturation of language-related brain regions (described in more detail in the Imaging section) might underlie the more severe thought disorder in younger compared with older children with the disease.

In addition to thought disorder, children with schizophrenia also have impaired basic linguistic skills (Blanchard et al., 2010; Caplan, Siddarth, & Gurbani, 2010;

Hollis, 2003; Kumra et al., 2000; Nicolson et al., 2000; Rhinewine et al., 2005). Although the severity of thought disorder and of linguistic deficits were significantly associated in 37 subjects with schizophrenia with a mean age of 13.6 (2.7) years, the patients with average linguistic skills (54%) also had thought disorder (Caplan et al., 2010). This finding, together with no relationship between thought disorder signs and other psychotic symptoms, premorbid symptoms, and IQ, suggested that thought disorder is a core feature of childhood onset schizophrenia (Caplan et al., 2010).

From the developmental perspective, it is essential to differentiate thought disorder from the difficult to understand or disorganized speech of children who have problems understanding language or expressing themselves due to a language disorder or intellectual disability. Since most clinicians do not have prior training on how to assess language and discourse skills in typically developing children of different ages, ruling in or out formal thought disorder poses a difficult diagnostic challenge. In such cases, referral to a speech and language therapist would help clarify the diagnosis.

Disorganized Behavior and Negative Symptoms

As previously noted, a reliable and valid assessment of disorganized behavior requires direct observation by a child mental health professional who knows how to determine possible reasons for young children's disorganized behavior. This nonspecific symptom can reflect fear, anxiety, anger, oppositionality, mania, encephalopathy (brain dysfunction/damage due to a neurological or metabolic disorder), or psychosis.

Regarding negative symptoms (Table 21.1), affective flattening and anhedonia are rare in children. In addition, what appears to be impoverished content of speech (alogia) in a young child might reflect a child's difficulty understanding the interviewer's questions due to immaturity, a language disorder, or intellectual disability. It often simply indicates that the interviewer is asking the child developmentally insensitive questions. Similarly, avolition (lack of motivation) in a young child could mean that an activity is boring, difficult, or not what the child wants to do. Therefore, mental health professionals need to use a developmental approach to clarify the nature of behaviors that appear to be negative symptoms in young children.

The Clinical and Research Implications

Comprehensive clinical assessment commensurate with a child's developmental level is essential to determine if hallucinations, delusions, and formal thought disorder represent schizophrenia, another type of psychosis, or other psychiatric disorders. Due to the developmental challenges involved in the diagnostic evaluations of young children, the psychotic nature of symptoms that appear to be related to other psychiatric disorders sometimes go unrecognized. Misdiagnosis and incorrect treatment of schizophrenia can have deleterious metabolic, neurological, and cognitive effects as described in the section on Treatment. Furthermore, since a diagnosis of schizophrenia is associated with a stigma, an incorrect diagnosis can cause significant repercussions for children and their families.

From the research perspective, misdiagnosis and the inclusion of a heterogeneous rather than a homogenous well-defined group of children in a study of this relatively rare disorder can result in erroneous or at best diluted findings. To help the reader face the diagnostic challenges, the next section describes the diagnostic categories that should be included in the differential diagnosis of psychotic symptoms and early-onset schizophrenia.

The Differential Diagnosis

The previous sections on hallucinations, delusions, and formal thought disorder emphasized the importance of ruling out normal developmental phenomena that might lead to a misdiagnosis of these psychotic symptoms. Two child population studies, one conducted in New Zealand on 788 children, aged 11 years (McGee, Williams, & Poulton, 2000) and one in Japan on 761 children, aged 11 and 12 years (Yoshizumi, Murase, Honjo, Kaneko, & Murakami, 2004), found hallucinations in 8% and 21% of these typically developing children, respectively. Using structured psychiatric interviews (McGee et al., 2000) and self-report instruments (Yoshizumi et al., 2004), these cross sectional studies found mainly anxiety, dissociation, and inattention in the children compared with those without hallucinations. Thus, the presence of hallucinations in a young child highlights the importance of a careful diagnostic assessment to first rule out more commonly occurring psychiatric disorders, as well as the more infrequent disorder, schizophrenia.

Application of clinical acumen to this diagnosis is further emphasized by two important prospective findings. The first is the relatively low rate of conversion to schizophrenia in follow-up studies of first episode psychosis in youth (Cannon et al., 2008). The second is the transient nature of atypical psychotic symptoms, particularly in children with a history of abuse and neglect, and evidence of dissociation (Hlastala & McClellan, 2005).

TABLE 21.4 Developmental Approach to Differential Diagnosis of Childhood and Adolescent Onset Schizophrenia

Disorder	Symptoms	Differentiate vs. schizophrenia (Sz)
Psychotic disorders		
Affective psychoses		
Depression	Irritability and angry mood	Appropriate facial expression of affect vs. inappropriate or incongruent affect in Sz
	Hallucinations, delusions, suicide	Mood congruent vs. bizarre content in Sz
	Negative signs	No affective flattening and anhedonia
Bipolar disorder	Mania, irritability, or angry mood	Appropriate facial expression of affect vs. inappropriate or incongruent affect in Sz
	Hallucinations, delusions	Mood congruent vs. bizarre content in Sz
	Distractibility, flight of ideas, increased motor activity	Mood congruent vs. association with internal preoccupations (hallucinations and delusions) in Sz
Schizoaffective	Irritability, anger, depression, mania	Appropriate facial expression of affect vs. inappropriate or incongruent affect in Sz
	Delusions, hallucinations, suicide	Mood congruent vs. bizarre content in Sz
Organic psychoses		
Epilepsy	Fixed hallucinations, delusions	Changing in Sz
	No loose association	Loose associations in Sz
	No negative signs	Negative symptoms evolve over time in Sz
Degenerative disorders	Hallucinations, delusions, thought disorder early in illness	Disorientation and significant loss of cognitive and linguistic skills in degenerative disorders vs. schizophrenia
Drug-induced psychosis	Often persecutory hallucinations, delusions	
	No negative signs	
Dissociative psychosis	Multiple past diagnoses	
	Threatening and protecting voice	Bizarre hallucinations, delusions in Sz
	No subjective distress	Significant subjective distress in Sz
Transient (psychotic-like) psychosis		
Schizophrenia, prodrome, spectrum disorder, psychosis NOS, muldimensionally impaired children, multiplex developmental disorder, schizotypal personality disorder	Vacillating reality testing for hallucinations, delusions	Does not meet frequency, duration, severity of Sz diagnostic criteria
Developmental disorders		
Autism spectrum disorders	Circumscribed preoccupations	Good reality testing vs. Sz
Fears and anxiety disorders		Good reality testing vs. Sz
Disruptive disorders		
Attention-deficit/hyperactivity disorder	Poor attention span	Impaired attention associated with hallucinations and delusions in Sz
Oppositional defiant disorder	Discipline related oppositionality	Hallucination and delusion induced oppositionality in Sz

Table 21.4 presents the diagnostic categories and disorders that should be included in the differential diagnosis of childhood onset schizophrenia. It highlights the symptoms of these disorders that pose diagnostic challenges from the developmental perspective and how to differentiate them from symptoms of schizophrenia.

Psychotic Disorders

Affective Psychosis. Depression with psychosis in middle childhood is frequently associated with the types of hallucinations and delusions found in schizophrenia but not with formal thought disorder (Ulloa et al., 2000). Whereas the content of hallucinations and delusions in affective psychoses (depression, bipolar disorder) is mood congruent, it is bizarre and unrelated to mood in schizophrenia. For example, a boy with psychotic depression who has delusions of guilt might experience auditory hallucinations that command him to kill himself because he is a bad person. A manic girl with a grandiose delusion that she is the world's best gymnast might have conversing auditory hallucinations in which she hears her peers talk about her amazing gymnastic skills. In contrast, a child with schizophrenia who believes that there is a slug in his nose (somatic delusion) might experience an auditory

command hallucination to kill himself to rid himself of the slug. The bizarre content of this hallucination is not mood congruent.

Negative signs are an inclusionary diagnostic criterion of both depression and schizophrenia. Young children with depression are often irritable and angry rather than sad, and do not present with the affective flattening found in adults and adolescents with depression and in youth with schizophrenia. Although depressed children rarely experience anhedonia, this symptom is prominent in adolescents with schizophrenia and in teen depression.

Negative symptoms could also represent side effects of high antipsychotic drug doses. Since young children rarely monitor and verbalize the side effects of drugs on their behavior, they are not good informants for this type of information. A parental report that the negative symptoms developed with increasing medication doses would support this diagnostic possibility. Persistent negative symptoms, together with worsening of hallucinations and delusions, in a young depressed child treated with an antidepressant drug, would suggest the likelihood of schizophrenia.

Schizophrenia is the eleventh leading cause for suicide in the general population with suicidal acts occurring in 20–50%, suicidal ideation in 50%, and eventual death by suicide in 4–13% of patients with schizophrenia (see review in Montross, Zisook, & Kasckow, 2005). There have been no studies to date, however, on the incidence and prevalence of suicidality in early-onset schizophrenia. Suicidal behavior needs to be assessed in every psychotic child. As for hallucinations and delusions, mood incongruency and bizarre content of suicidal ideation help confirm schizophrenia rather than an affective disorder.

Unlike their adolescent counterparts, however, young children with schizophrenia do not usually think a lot about death and dying, spontaneously tell mental health professionals about suicidal thoughts and plans, nor confirm these symptoms when asked about them in front of their parents. Due to fear that their parents will be angry with them if they have these symptoms, it is necessary to evaluate them without their parents to ask them about suicidal ideation and plans.

Dissociative Psychosis. In addition to a past psychiatric history of unsuccessfully treated prior multiple psychiatric diagnoses and abuse (physical, sexual, or emotional), the auditory hallucinations of youth with dissociative psychosis usually involve familiar people from the child's life with one threatening and one protecting voice (Hornstein & Putnam, 1992). Visual hallucinations appear as apparition-like images (Hornstein & Putnam, 1992). In contrast to children with other psychotic disorders, children with dissociative psychosis do not appear to be distressed by their hallucinations. Delusions, other than thought withdrawal and insertion, and formal thought disorder are not features of this disorder (Hornstein & Putnam, 1992).

Organic Psychoses. Among the neurological disorders, pediatric epilepsy is infrequently associated with psychosis during (ictal), after (post-ictal), and between seizures (interictal) (see review in (Kanner & Dunn, 2004)). Ictal psychosis includes unchanging, stereotyped, unimodal (involving one sensory system), and subjectively distressing hallucinations, as well as delusions (mainly forced thinking). Unlike schizophrenia, affective psychoses, and dissociative psychosis, children with ictal psychosis do not recall the content of their hallucinations or delusions unless they occurred during an aura that was not followed by a generalized tonic-clonic seizure.

Similar to schizophrenia, children with interictal psychoses have multimodal hallucinations that vary in content and form, delusions, and formal thought disorder (Caplan, Shields, Mori, & Yudovin, 1991). However, they do not have negative signs or mood congruent psychotic symptoms. Postictal psychosis is rare in children (Kanner & Dunn, 2004).

Psychosis can occur in early stages of neurological disorders, such as acute disseminated myelitis (Krishnakumar, Jayakrishnan, Beegum, & Riyaz, 2008) and subacute sclerosing panencephalitis (Caplan, Tanguay, & Szekely, 1987), and in medical disorders, such as systemic lupus erythematosus with involvement of the central nervous system (Sibbitt et al., 2002). At disease onset, the hallucinations, delusions, and formal thought disorder are stereotyped and pervasive in contrast to the variable and nonstereotyped form and content of psychotic symptoms in schizophrenia. They disappear as the illness worsens with evidence for disorientation, confusion, and loss of cognitive functions and language.

Delirium, secondary to a medical illness with central nervous system effects or a primary neurological illness, presents with sudden confusion together with fluctuating awareness (waxing and waning of orientation, cognition, and language skill; see review in Smith, Brink, Fuchs, Ely, & Pandharipande, 2013). Youth with schizophrenia are usually oriented (time, place, situation) and their level of awareness does not fluctuate. Variable impairment of both receptive and expressive language with disorganized, disjointed, or incoherent speech and in severe cases, loss of speech, suggest delirium rather than schizophrenia.

Visual hallucinations without auditory hallucinations can be seen in delirium, but not in schizophrenia. If a child talks to herself or has a focused look associated with mumbling, picking, fear, or laughter, this might suggest that she has delirium with auditory or visual hallucinations. However, as previously mentioned, a reliable and valid assessment of hallucinations can be done only with a child who can verbally confirm the hallucinatory experience.

Iatrogenic Psychoses. Corticosteroids can cause psychosis with persecutory delusions and auditory hallucinations with or without altered conscious level and disorientation (see review in Stuart, Segal, & Keady, 2005). Adderall XR, atomoxetine, modafinil, oral and transdermal methylphenidates can trigger persecutory, visual, and tactile hallucinations in children (Mosholder, Gelperin, Hammad, Phelan, & Johann-Liang, 2009). Several mood stabilizers, also used as antiepileptic drugs (ethosuximide, levetiracetam, phenytoin, topiramate, vigabatrin, zonisamide, and felbamate) can induce psychosis in youth with epilepsy (see review in Caplan & Bursch, 2012) but not in youth with bipolar disorder.

Transient Psychosis and Psychotic-like Disorders. Psychosis not otherwise specified (NOS), schizophrenia prodrome, schizophrenia spectrum disorder, multidimensional impairment, multiplex developmental disorder, and schizotypal personality disorder have several features in common. They include children or adolescents who do not meet diagnostic criteria for schizophrenia in terms of the duration, frequency, severity, and prevasiveness of symptoms. For example, an adolescent feels that the world in which he lives is a set with actors (like the *Truman Show*) who are there to observe him. Sometimes he thinks this is his misperception while at other times he is convinced that his life is a setup. Vacillating impairment of reality testing, as in this case, is a feature of the prodromal syndrome, described in detail in (Miller et al., 2003).

The large number of diagnostic categories included under transient psychotic disorders might also reflect the developmental difficulties involved in diagnosing early-onset schizophrenia. In addition, clinicians are reticent to make this diagnosis because of its stigma; the metabolic and neurological side effects of antipsychotic drugs; as well as evidence that children followed for two or more years no longer meet diagnostic criteria for schizophrenia (see review in McClellan & Stock, 2013) and that only 35% of 291 prodromal youth followed convert to schizophrenia (Cannon, 2008).

Youth with schizoaffective disorder meet criteria for schizophrenia but also have prominent affective symptoms. The dimensional versus categorical debate on the diagnosis of schizophrenia, schizoaffective psychosis, and affective psychoses is evident in the adult but not the child literature (see review in Abrams, Rojas, & Arciniegas, 2008). The dimensional theory proposes that these three disorders differ in the extent of psychotic versus affective symptoms. Thus, schizophrenia involves mainly positive psychotic symptoms whereas affective psychoses have prominent affective symptoms. But both affective and positive psychotic symptoms are evident in schizoaffective disorder.

The categorical theory maintains that each of these three diagnostic categories have separate characteristic features. Although adult studies find poor diagnostic reliability for schizoaffective psychosis (see reviews in Abrams et al., 2008), this does not appear to be the case in youth with schizoaffetive disorder (Frazier et al., 2007).

The NIMH group compared children with multidimensional impairment to treatment resistant youth with schizophrenia (Nicolson et al., 2001). In addition to hallucinations and delusions, 19 children with this diagnosis had impaired control of impulse, attention, and affect, as well as poor interpersonal skills despite their wish to have friends. They also had variable developmental delay and autistic symptoms. At the 8-year follow-up, their diagnoses included schizoaffective disorder ($N = 1$), psychosis NOS ($N = 15$), schizotypal personality disorder ($N = 1$), as well as comorbid bipolar disorder ($N = 12$) and major depression ($N = 4$).

The heterogeneous nature of these additional axis I diagnoses, their prominent affective component and psychotic symptoms in most of the subjects at follow-up question the validity of this diagnostic entity. Prior to the introduction of the prodromal syndrome and multidimensionally impaired diagnoses, researchers diagnosed these children with schizotypal personality disorder (Asarnow, 2005) and multiplex developmental disorder (van der Gaag, Caplan, van Engeland, Loman, & Buitelaar, 2005).

Developmental Disorders

Autism Spectrum Disorder. This diagnostic category poses diagnostic challenges when children's circumscribed preoccupations involve imagination and fantasy. In such cases clinicians should determine if the child is aware of the imaginary nature of his preoccupations, and whether the child will act on them. For example, a boy repeatedly thought he was in a time machine. When in the time machine, he talked about and enacted relevant scenes, events, and stories. He was well aware that there is no such thing as a time machine and that this was his imagination. But, he also repeatedly

drew pictures with snakes, monsters, the devil, and people in coffins. He became scared, agitated, and nonverbal when asked about these drawings. Subsequently he was able to say that the devil threatened to place him alive in the coffin with the snakes and monsters. He believed that they were watching him all the time so that they could catch him. This child met diagnostic criteria for both Asperger syndrome and schizophrenia by virtue of his visual and auditory hallucinations, as well as persecutory delusion.

Anxiety Disorders

These disorders are included in the differential diagnosis to emphasize that not all forms of worry, repeated thoughts, or difficulties separating from parents mean a child has a generalized anxiety disorder, obsessive-compulsive disorder, or separation anxiety disorder, respectively. Hallucinations or delusions might underlie these symptoms.

Attention Deficit Hyperactivity Disorder (ADHD)

Although concentration problems are found in ADHD, some children confirm these difficulties when their attention is distracted by hallucinations and recurrent delusions.

Oppositional Defiant Disorder

Irritable affect and associated oppositional behavior in response to hallucinations and delusions might be incorrectly diagnosed as oppositional defiant disorder if their underlying psychotic symptoms are not apparent.

Summary and Conclusions

- A developmental approach is essential for a reliable and valid diagnosis of:
  - Positive psychotic symptoms: Hallucinations, delusions, formal thought disorder
  - Negative psychotic symptoms: Affective flattening, anhedonia, avolition, alogia
  - Disorganized behavior
- The differential diagnosis of childhood onset schizophrenia includes a wide range of psychiatric disorders.
- An accurate diagnosis is a critical prerequisite for:
  - Treatment given the severe adverse effects of antipsychotic drugs
  - To ensure reliable and valid research findings

COGNITION

Low IQ, a central feature of schizophrenia, has led to the suggestion that schizophrenia is a cognitive illness (Kahn & Keefe, 2013). Some researchers consider impaired executive functions (attention, abstract thought, planning/organizing, inhibition and self-monitoring) as core illness deficits (see review in Neill & Rossell, 2013). Others maintain that they reflect lower level or general cognitive deficits (see review in Neill & Rossell, 2013).

Similar to adults with schizophrenia (see review in Kahn & Keefe, 2013), 54 childhood and adolescent onset patients, aged 10–18 years, in a North American multisite study had global cognitive dysfunction with mean IQ scores that were 2 standard deviations lower than 52 normal controls (Rhinewine et al., 2005). In addition as found in adults with this illness, during the two years before and 1.7 years after onset of psychotic symptoms, 31 early-onset youth with schizophrenia in the NIMH cohort had an irreversible decrease in IQ with no subsequent changes during the 13 years after psychosis onset (Gochman et al., 2005).

In contrast, despite no change in symptoms and in both the type and dose of medication, 20 patients from the Maudsley Early-onset Schizophrenia Study with onset of schizophrenia before age 17 had stable intellectual functioning and planning ability over a 4 (+/- 1.08) year period (Frangou, Hadjulis, & Vourdas, 2008). Methodological differences, namely, treatment resistance in the NIMH subjects and the small sample of the Maudsley study might underlie these different findings.

But unlike adult schizophrenia, there also appears to be a downhill course over time in aspects of cognition other than IQ. Frangou et al. (Frangou et al., 2008) reported deterioration in verbal memory and learning, attentional control, and perseverative errors during their 4-year follow-up study of 20 adolescents with schizophrenia. Similarly, a 5-year follow-up study of 17 youth with schizophrenia revealed a significant increased impairment of attention and set shifting (Jepsen et al., 2010). Thaden et al. (Thaden et al., 2006) found poor performance with increasing age and task difficulty on a Continuous Performance Test in 59 adolescents with schizophrenia compared with 55 control subjects. Involvement of the dorsolateral prefrontal region in adult schizophrenia (see review in Fornito, Yucel, Patti, Wood, & Pantelis, 2009) and maturation of this brain region during adolescence (Lenroot & Giedd, 2006; Muftuler et al., 2011) might underlie the age-related increase in executive function deficits in adolescents with schizophrenia.

Regarding clinical variables, the severity of cognitive deficits is associated with negative symptoms and poor premorbid adjustment involving academic achievement (Rhinewine et al., 2005) and social isolation (Thaden et al., 2006). The type of diagnosis, whether schizophrenia compared with schizoaffective disorder (Hooper et al.,

2010) or schizophrenia versus psychosis NOS (Kumra et al., 2000), is unrelated to the profile and severity of cognitive impairments.

Antipsychotic drugs also appear to have a minor effect on cognitive function. A large multicenter double blind randomized controlled study of 116 early-onset schizophrenia and schizoaffective disorder patients treated with olanzepine, molindone, and risperidone showed only a modest effect on neurocognitive impairments (Frazier et al., 2012).

Family and clinical high-risk studies shed additional light on the central role of cognition in schizophrenia. The parents of 79 children with schizophrenia had significantly more motor, attention, and visual spatial processing impairments compared with the parents of 190 children with ADHD and 115 community controls in the UCLA Family Study (Asarnow et al., 2002). Using the same motor speed test as in Asarnow et al. (Asarnow et al., 2002), 67 parents of the treatment resistant childhood onset schizophrenia NIMH probands performed similar to 76 parents of community controls (Gochman et al., 2004). They also did not differ from the parents of the community controls on general intelligence, working memory, and vocabulary tests. Sample size differences in the control groups of these studies, 114 in Asarnow et al. and 76 in Gochman et al., might have contributed to the different motor speed findings.

Unlike their parents, 24 siblings (mean age of 19.3 years (SD = 7.0)) of the NIMH probands with schizophrenia had impaired motor speed compared with the 38 community controls, aged 17.8 years (SD = 9.0). De La Serna (de la Serna et al., 2011) also found low IQ index, logical memory, and perceptual organization scores but no significant differences in performance on visual tasks in 26 nonpsychotic siblings, aged 7–16-years old, compared with 33 control subjects.

The importance of familial loading for schizophrenia and cognition is apparent in the children of parents with schizophrenia. Twenty-five children, aged 9–12 years, each with a parent who had schizophrenia, had borderline to mildly impaired working memory and poor response inhibition during a motor task that continued at the 2.6 year follow-up (Ross, Wagner, Heinlein, & Zerbe, 2008). De la Serna (de la Serna et al., 2011) also described significantly lower IQ index, poor logical and visual memory, as well as worse perceptual organization scores in 20 offspring of schizophrenia parents, aged 7–16 years, compared with aged-matched 33 healthy control subjects. Although the offspring groups in both the Ross et al. and de la Serna et al. studies had high ADHD rates, similar cognitive deficits in those with and without ADHD suggest that ADHD did not account for the cognitive findings.

Finally, adolescents at clinical or high risk for schizophrenia (schizophrenia prodrome) have significantly lower verbal IQ, verbal memory and learning, as well as attention scores than controls but intermediate scores between those of individuals with first episode psychosis and controls (see review in Addington & Barbato, 2012). Although stable over time, these cognitive impairments do not predict conversion to psychosis.

Yet, both global and specific cognitive deficits in childhood and adolescence appear to be risk factors for adult onset schizophrenia (see meta-analysis in Dickson, Laurens, Cullen, & Hodgins, 2012). In fact, children ($N = 28$), aged 9–12 years, with a triad of putative antecedents for schizophrenia (Laurens et al., 2007) (Table 21.5) who had average IQ, performed significantly worse on tests of scholastic achievement, verbal memory, visual memory, working memory, verbal fluency, and inhibition than 27 typically developing children (Cullen et al., 2010).

Summary and Conclusions

- Is schizophrenia a cognitive disorder?
  - Youth with schizophrenia have low IQ, slow processing speed, and impaired verbal memory and learning, visual spatial, and motor skills.

TABLE 21.5 Childhood Triad of Putative Antecedents[1] of Adult Onset Schizophrenia

Symptom	Type
Psychotic-like experiences	Thought reading
Informant = child	Special messages
Source = interview	Being followed or spied on
	Hear voices
	Body changes that cannot be understood
	Under control of special power
	Mind reading
	Has special powers
	Sees things no one else can
Developmental delay and abnormalities	Motor and speech
Informant = parent, professional	Current coordination, unsteadiness problem
Source = questionnaire	
Social	Emotional symptoms
Informant = child, parent	Conduct problems
Source = Strengths & Difficulties Questionnaire[2]	Hyperactivity
	Peer problems

[1] Described in Laurens et al. (2007)
[2] Goodman (2001)

  - As they get older, they also have impaired attention and executive function.
  - After the initial decline in IQ and age-related appearance of executive function deficits, the cognitive deficits are stable over time.
  - The severity of cognitive deficits is related to negative symptoms and poor premorbid adjustment.
- Similar cognitive deficits are evident in:
  - First-degree relatives (parents, siblings, offspring)
  - Youth at clinical risk for schizophrenia
  - Children with a triad of putative antecedents of schizophrenia
- Studies are warranted to determine:
  - How cognition and its impairment differentially contribute to resilience and vulnerability to schizophrenia
  - The short- and long-term effects of deficit focused cognitive, linguistic, and educational rehabilitation

SOCIAL COGNITION

A meta-analysis of studies conducted to date on social cognition in adult schizophrenia found significant impairment compared with controls in theory of mind, emotion processing, emotion perception, and social perception (Savla, Vella, Armstrong, Penn, & Twamley, 2012). Social cognition impairments in these patients were significantly associated with duration of illness and inpatient status (Savla et al., 2012), as well as negative symptoms, disorganization, and cognitive deficits (Mancuso, Horan, Kern, & Green, 2011).

Social cognition studies have not been conducted in early-onset schizophrenia. However, a large group of 79 ultra high-risk subjects and 30 first episode psychosis patients, aged 13–25 years, had worse emotion recognition of both facial emotions and prosody than 30 control subjects (Amminger et al., 2012). Similar deficits in emotion processing, theory of mind, and social relationship perception in 54 adolescent and young adult prodromal subjects (18.25 (3.12) years) vs. 34 controls (18.95 (2.91) years) suggest impairments of these aspects of social cognition prior to the onset of schizophrenia (Green et al., 2011). Furthermore, the clinical importance of social cognition is highlighted by the relationship, above and beyond the effects of ongoing psychotic symptoms, of baseline social cognition measures with the 12-month follow-up functional outcome (work, social, and independent living) of 55 first episode psychosis patients (Horan et al., 2011).

Summary and Conclusions

- Impaired social cognition is evident in adult schizophrenia, ultra high-risk, prodromal, and first episode psychosis patients.
- Its association with clinical severity and functional outcome emphasizes the need for social cognition studies in early-onset schizophrenia.

RISK FACTORS

Identifying the risk factors and premorbid features of schizophrenia (Table 21.6) is important because together

TABLE 21.6 Risk Factors for Schizophrenia (Sz)

Stage	Risk Factors	Early-onset	Adult Onset
Perinatal	Infections	Not studied	Influenza, Herpes simplex Type 2, Toxoplasma gondi, rubella, measles, and upper respiratory tract infections
	Obstetric	Related to speech and language delay in Sz but not to increased likelihood of diagnosis	Fetal hypoxia
Infancy	Development	Delayed motor, speech milestones	Delayed motor, speech milestones
		Deviant language	Erratic infant development (pandysmaturation)
Childhood	Motor		Poor gross and fine motor coordination, unusual movements
	Language		Poor verbal skills
	Social	Autism spectrum disorder symptoms	Solitary, withdrawal
	Academic	Poor premorbid academic adjustment	Poor school performance
	Environmental		
	Demographic	Poverty, urban	Poverty, urban
	Cultural	Immigrant status, minority	Immigrant status, minority
	Adversity	Not yet studied	Trauma, abuse, neglect
	Cannabis	Toxic effect, self medication, poor outcome	Toxic effect, earlier onset

with family history, they act as clinical markers that can facilitate early detection of individuals at risk and of those who might be resilient for the disorder. In addition, they have developmental implications, and help predict the severity, course, and outcome of the illness (see review in Cole, Apud, Weinberger, & Dickinson, 2012). But, only few retrospective studies have examined the risk factors and premorbid features of early-onset schizophrenia. In contrast, several large prospective birth cohort and offspring studies have identified the perinatal, infancy, and childhood risk factors and premorbid features of adult onset schizophrenia and conversion to schizophrenia in youth with the schizophrenia prodrome. Given the importance of early detection and treatment of children and adolescents at risk for schizophrenia, this section includes the findings of these studies.

Perinatal Factors

Early-onset Schizophrenia

Since Mednick's pioneer Finnish birth cohort study demonstrated increased influenza A2 during the second trimester of pregnancy of individuals hospitalized for schizophrenia in adulthood (Mednick, 1988), numerous studies have examined the role of perinatal factors in schizophrenia (see review in Brown & Derkits, 2010). Only two retrospective studies have been conducted to date on obstetric complications in children and adolescents with schizophrenia. The NIMH study found no significant differences in the number of obstetric and perinatal complications in 36 early-onset schizophrenia patients and their 35 nonpsychotic siblings (Nicolson, Malaspina, Giedd, Hamburger, Lenane et al., 1999). Based on parent interviews and birth records, Margari et al. also found no significant between group differences in the prepartum, peripartum, and postpartum complications of 21 Italian children with schizophrenia and 21 children with migraine (Margari et al., 2011).

The NIMH study also found delayed speech and language development in the children with refractory schizophrenia who had more obstetric complications compared with those with normal language development (Nicolson et al., 2000). Unlike the children with normal speech and language milestones, those with more obstetric complications also had higher familial loading for schizophrenia.

Birth weight, an indirect measure of the health of the intrauterine environment, reflects the severity of prenatal adversities (Haukvik et al., 2013) that might potentially impact behavior, cognition, and brain development. It is related to vulnerability for impaired academic, nonacademic, and physical education performance in adolescents at genetic risk for schizophrenia (Forsyth et al., 2012).

Adult Onset Schizophrenia

Prospective birth cohort studies have demonstrated greater likelihood of schizophrenia in individuals exposed to influenza, Herpes simplex Type 2, Toxoplasma gondi, rubella, measles, and upper respiratory tract infections. The window for vulnerability appears to be the first half of pregnancy and particularly early on in pregnancy (see review in Brown & Derkits, 2010).

A higher number of obstetric complications also increased the likelihood of schizophrenia in patients with onset of the disorder prior to but not after age 17 in the Philadelphia site of the National Collaborative Perinatal Project (Cannon et al., 2000). These age-related findings together with no schizophrenia in the 73 probands of 63 siblings, despite their obstetric complications, suggested a specific vulnerability for obstetric complications in individuals with earlier onset schizophrenia.

The findings from other Collaborative Perinatal Project sites and birth cohort studies confirm the importance of obstetric complications in individuals with genetic risk for schizophrenia (see review in Brown, 2011). In addition, perinatal infections and obstetric complications are also more prevalent in infants born to mothers with schizophrenia (Suvisaari et al., 2012).

But, the presence and number of perinatal complications in birth cohort (Cannon et al., 2002; Rosso et al., 2000) and offspring studies (Forsyth et al., 2012; Marcus, Hans, Auerbach, & Auerbach, 1993; McNeil, Fish, & Schubert, 2011) were unrelated to impaired receptive language skills, delayed motor development, and poor motor coordination in subjects diagnosed with schizophrenia in adulthood. Findings are also inconsistent regarding the association of birth weight with adult onset schizophrenia in these studies (see review in Fineberg, Ellman, Buka, Yolken, & Cannon, 2012).

Summary and Conclusions

- Although obstetric complications are not increased in early-onset schizophrenia, they are related to delayed language development and a family loading for schizophrenia.
- Low birth weight is associated with poor academic, nonacademic, and physical education performance in adolescents with a familial loading for schizophrenia.
- Perinatal infections and obstetric complications, not birth weight, increase the likelihood of schizophrenia in adult subjects with a family history.

- The different child and adult study findings reflect small sample size, retrospective study design, different obstetric complication categories, and items in the child studies, as well as the refractory illness of the NIMH study subjects.
- Prospective birth cohort studies are warranted to determine if perinatal complications and birth weight are associated with vulnerability for early-onset schizophrenia.

Risk Factors During Infancy

Early-onset Schizophrenia

Based on chart reviews and parents' retrospective reporting, delayed motor development is found in 72% (Watkins, Asarnow, & Tanguay, 1988) of these patients and language delay or deviant language in 44–72% (Hollis, 1995; Nicolson et al., 2000).

Adult Onset Schizophrenia

Pandysmaturation, defined as delayed cranial development, together with delay or erratic development of at least one motor milestone, differentially predicted schizophrenia outcome in the offspring of mothers with schizophrenia compared with the offspring of mothers with other psychiatric diagnoses or affective disorders and mothers without prior psychiatric diagnoses or psychosis (Fish & Kendler, 2005; McNeil et al., 2011). The Swedish High-risk Project study demonstrated that among the 75 offspring of mothers with schizophrenia those with pandysmaturation were 34 times more likely to have schizophrenia at age 22 than the offspring of 75 mothers with affective disorders and 91 mothers with no psychiatric diagnoses (McNeil et al., 2011). Since controlling for genetic risk for schizophrenia attenuated the risk, these authors concluded that pandysmaturation reflects a genetic risk for schizophrenia.

In contrast to subjects with normal development, the Dunedin birth cohort subjects with pan-developmental delay involving motor, language, and social skills self-reported psychotic symptoms at age 11 met criteria for a schizophrenia spectrum disorder diagnosis at age 26 (Cannon et al., 2002). Slow motor development, in particularly walking, and delayed onset of speech were evident in the 30 individuals diagnosed with schizophrenia between age 16 and 43 in the British Medical Research Council National Survey of Health and Development survey of 13,687 births in England, Scotland, and Wales in 1946 (Jones, Murray, Rodgers, & Marmot, 1994).

Likewise, in the 1966 Northern Finland birth cohort (N = 9901) followed for 31 years, age at attainment of milestones (standing, walking, speech, toilet training) was linearly associated with hospital registry diagnosis of schizophrenia ($N = 100$) and other psychoses ($N = 55$) (Isohanni et al., 2001). Furthermore, the previously described (see section on Cognition and Table 21.5) large study that screened for putative antecedents of schizophrenia in 548 low-income U.K. youth, aged 9–12 years, identified speech/motor delayed development in 9.2% of boys and 4.1% of girls (Laurens et al., 2007).

New evidence also highlights the possible role of perinatal variables on infant vulnerability for core deficits of schizophrenia, such as abnormal sensorimotor gating (Ross et al., 2013). Abnormal sensorimotor gating, reduced inhibition or gating of the P50 component of the cerebral auditory evoked response to the second of paired sounds given 500 msec apart, occurs in infants of mothers with psychosis (Hunter, Kisley, McCarthy, Freedman, & Ross, 2011). Genes associated with schizophrenia, including CHRNA7 and neuroregulin, phosphatidylethanolamine-(PEMT) (Ross et al., 2013), and environmental factors, such as the pregnant mother's diet, determine fetal levels of acetylcholine and hippocampal $\alpha 7$ nicotinic receptor density. Phosphatidyl choline dietary supplementation during and after pregnancy increases the acetylcholine level and improves sensory gating in the infants of healthy mothers both with and without the CHRNA7 gene compared with placebo treated mothers (Ross et al., 2013). Thus, phosphatidyl choline supplementation, a perinatal environmental factor, might prevent the development of aberrant attention even in individuals with a genetic predisposition (CHRNA7 gene) for poor sensorimotor gating and schizophrenia (Ross et al., 2013).

Summary and Conclusions

- Children with schizophrenia, high-risk offspring of mothers with schizophrenia, and children at risk for adult onset of schizophrenia, have delayed motor and speech milestones.
- Abnormal sensorimotor gating during early infancy might normalize with phosphatidyl choline supplement even in the presence of a genetic predisposition to schizophrenia.

Childhood Risk Factors

Abnormal Development

Early-onset Schizophrenia. Social withdrawal during childhood and adolescence appears to be a specific vulnerability factor for schizophrenia. A retrospective chart review of 101 children, aged 7–13 years, found significantly

more children with premorbid social impairment in the 61 who developed schizophrenia between age 14 and 17 than in the 49 with other types of psychosis (Hollis, 2003). Additional retrospective reports by parents and review of medical charts describe premorbid symptoms of autism spectrum disorders in 25–87% of children with schizophrenia (Margari et al., 2011; Nicolson et al., 2000; Watkins et al., 1988).

Adult Onset Schizophrenia. Social maladjustment at age 4 and 7 years (Bearden et al., 2000), parent-based reports of social withdrawal between ages 9 and 14 years in birth cohort studies and in youth with putative antecedents of schizophrenia (see meta-analysis in Matheson et al., 2013), and social withdrawal during childhood in young adult first episode schizophrenia patients (Tarbox, Brown, & Haas, 2012) revealed a significantly increased likelihood of schizophrenia during adulthood. The British Medical Research Council National Survey researchers also noted more individuals with solitary play and speech difficulties at age 4 and 6 years in the preschizophrenic subjects than in the controls (Jones et al., 1994).

Compared with the 3, 5, and 9-year old healthy controls, the Dunedin study subjects who later developed schizophrenia had more than one soft neurological sign and performed poorly on standard tests of motor skill (Cannon et al., 2002). Subjects who met criteria for schizophrenia during adulthood in the Philadelphia cohort of the Collaborative Perinatal Project birth cohort and their unaffected siblings had deviant motor coordination at age 7 years, unusual movements (tremors, tics, spasms, or athetoid movements of the head and neck, arms and shoulders, hands, legs and feet, or trunk) at age 4 and 7, and poor language scores (Bearden et al., 2000; Rosso et al., 2000). Similarly, abnormal development of gross motor skills, verbal memory, and attention (Erlenmeyer-Kimling et al., 2000), as well as impaired motor coordination (Marcus et al., 1993; Schiffman et al., 2009) during middle and late childhood was found in the offspring of parents with schizophrenia.

Poor Academic Performance and Cognition

Early-Onset Schizophrenia. As previously mentioned (see section on Cognition), the U.S. multisite early-onset schizophrenia study reported worse premorbid academic adjustment among 54 adolescents with schizophrenia with significantly lower cognitive scores and negative symptoms after onset of the disorder (Rhinewine et al., 2005).

Adult Onset Schizophrenia. The Philadelphia Perinatal Collaborative birth cohort study reported significantly lower picture arrangement, vocabulary, and coding scores on the Wechsler Intelligence Scale for Children scores at age 7 in 32 subjects diagnosed with schizophrenia during adulthood and their 25 unaffected siblings compared with 201 nonpsychiatric comparison subjects (Niendam et al., 2003). The premorbid patients, however, had significantly lower coding scores than their unaffected siblings.

Summary and Conclusions

- Abnormal social development during early childhood is evident in early-onset schizophrenia and in individuals at risk for adult onset schizophrenia.
- Motor abnormalities are found in middle and late childhood in individuals at risk for adult onset of the disorder and in the offspring of schizophrenia parents.
- Additional premorbid features of early-onset and adult schizophrenia include poor school performance and low IQ.

Demographic and Cultural Factors

Based on the Israeli Army Draft Board and Psychiatric Registry, high population density (Weiser et al., 2007); perceived poor family functioning (Weiser, Reichenberg, et al., 2008), lower socioeconomic status (Goldberg et al., 2011), and acculturation (Weiser, Werbeloff, et al., 2008) are important premorbid environmental risk factors for psychiatric admission of 15–18-year old males with schizophrenia. Population and case-control studies have identified similar premorbid demographic risk factors for schizophrenia onset in adults in several countries (see review in Brown, 2011). These include being urban vs. rural, a first-, second-, and third-generation migrant, an ethnic minority in a nonethnic neighborhood, non-White in a predominantly White environment, poor, and experiencing cultural disparity in the dominant culture. Putative childhood antecedents of adult onset schizophrenia also occur at a significantly higher rate in African-Caribbean youth than in White U.K. youth irrespective of migration status (Laurens, West, Murray, & Hodgins, 2008).

Summary and Conclusions

- Urban environment, poverty, minority or immigrant status, and poor family functioning are risk factors for early-onset schizophrenia.

Childhood Adversity: Trauma, Abuse, and Neglect

Early-Onset Schizophrenia

In a large Irish study of 1,112 school-based adolescents, aged 13–16 years, childhood trauma (physical abuse and

bullying) was bidirectionally associated with psychotic symptoms over a 3- and 12-month follow-up (Kelleher, 2013). There was a dose dependent relationship between the severity of bullying and the risk for psychotic experiences. Thus, the incidence of psychosis gradually decreased with the cessation of bullying.

Toth et al.'s thought disorder findings on a subgroup of 242 maltreated and 158 nonmaltreated children, aged 10–12 years, imply a possible role of childhood adversity on core symptoms of schizophrenia (Toth, Pickreign Stronach, Rogosch, Caplan, & Cicchetti, 2011). The 91 children who experienced abuse (mainly physical abuse, neglect, and emotional maltreatment) had significantly more illogical thinking and mean scores in the clinical range compared with the 43 nonmaltreated and age-matched children (6.8–13.4 years). The significant association of younger age and more abuse incidents with higher illogical thinking scores implied possible early effects of abuse on the development of language-related brain regions, such as the superior temporal gyrus and inferior frontal gyrus, that are involved in the thought disorder of childhood schizophrenia (Borofsky et al., 2010; see details in the Imaging section).

Supporting Toth et al.'s findings, a two-year prospective study demonstrated a higher rate of abuse, neglect, and dissociation in 20 adolescents diagnosed at baseline with atypical psychotic symptoms compared with 23 with schizophrenia (Hlastala & McClellan, 2005). However, the atypical psychosis group met criteria for PTSD and depression but not for psychosis two years after being diagnosed with atypical psychosis.

Clinical Risk Studies

Several international large-scale studies have confirmed an association between abuse during childhood and psychotic symptoms in adolescents, young adults, and older adults. One third of a large Australian sample of first episode psychosis patients ($N = 704$), aged 15–29, had a history of physical or sexual abuse during childhood, as well as past psychiatric diagnoses, including PTSD, depression, substance abuse, suicide attempts, and poor premorbid functioning (Conus, Cotton, Schimmelmann, McGorry, & Lambert, 2010). An Australian prospective study of 233 subjects at ultra high risk for psychosis, aged 15–30 years, over a mean period of 7.5 years, identified a childhood history of sexual abuse but no other types of trauma as a significant risk factor for transition to psychosis (Thompson et al., 2013). Similarly, a Dutch prospective study over a three-year period on 4045 subjects, aged 18–64 years, described a significant association of childhood abuse reported at baseline with the onset of positive psychotic symptoms (Janssen et al., 2004).

Among 5782 subjects, aged 15–64 years from the US National Collaborative Survey (childhood trauma) and 8582 subjects, aged 16–74 years from the British Psychiatric Morbidity Survey, two or more traumas predicted psychosis in a dose dependent relationship (Shevlin, Houston, Dorahy, & Adamson, 2008). Of interest, childhood physical and sexual abuse in the US sample but physical injury and exposure to domestic violence during childhood in the U.K. study increased the risk for psychosis. Underscoring the importance of the number of traumatic events, a recent meta-analysis of large-scale cross sectional and prospective cohort studies confirmed a dose dependent relationship of childhood adversity (physical, sexual, emotional abuse, and neglect) with psychosis (i.e., psychotic disorder, schizophrenia, or schizoaffective disorder) (Varese et al., 2012).

Finally, a retrospective report of childhood abuse was associated with current positive psychotic-like symptoms in 533 young adults who were Met carriers of the Val66Met brain derived neurotrophic factor (BDNF) compared with the Val homozygotes (Alemany et al., 2011). These findings, together with evidence for gene-environment interaction in determining resilience or maladaptive depression, rigid personality, or substance abuse in maltreated children (Cicchetti & Rogosch, 2012) underscore the need for markers of vulnerability for psychosis following childhood maltreatment.

Summary and Conclusions

- Childhood adversity (trauma, abuse, or neglect) is associated with:
  - Illogical thinking during childhood
  - Adult onset schizophrenia, particularly in Met carriers of the Val66Met BDNF

Cannabis

The psychotomimetic effects of cannabis trigger onset of schizophrenia. Despite earlier age of onset in adult studies (De Hert et al., 2011), 468 cannabis users, aged 14–29 years, did not have a significantly earlier onset than the 157 noncannabis users with first-episode psychosis (Schimmelmann et al., 2011). Within the cannabis user subgroup, however, subjects who began using cannabis at age 14 years or earlier had a significantly earlier onset of psychotic symptoms than those with use after age 14.

Regarding the severity of psychosis, cannabis use at baseline was also related to higher illness-severity, lower

psychosocial functioning, less insight, lower premorbid functioning, and longer duration of untreated psychosis. But, only those youth with continued cannabis use during the follow-up period had a worse long-term outcome. Interestingly, most of the subjects in this study stopped using cannabis once their condition improved with antipsychotic treatment. Thus, there is a potential confounding among the onset of psychotic symptoms, the drug's psychotomimetic effects, and its use to self-medicate psychotic symptoms.

Among environmental factors, urbanicity (Kuepper, van Os, Lieb, Wittchen, & Henquet, 2011) and maltreatment (Harley et al., 2010), risk factors for schizophrenia, described under demographic risk factors, are also more frequent in individuals with schizophrenia who use cannabis than in nonusers. But both cannabis use and trauma were independently related to the risk of experiencing psychotic symptoms in 211 Irish youth, aged 12–15 years (Harley et al., 2010).

Two large prospective cohorts from the Greek National Perinatal Study ($N = 1636$) and the Netherlands Mental Health Survey and Incidence Study (NEMESIS) ($N = 4842$), also demonstrated that the psychosis inducing effect of cannabis use at age 19 was stronger in the subjects who experienced abuse at age 7 (Konings et al., 2012). In the Greek sample the abuse was limited to physical punishment (spanking of variable frequency) but it included emotional, physical, psychological, or sexual abuse in the Dutch sample.

To examine genetic effects and their interaction with these environmental factors, the Dutch Genetic Risk and Outcome in Psychosis (GROUP) investigators examined clinical and subclinical psychotic symptoms (schizotypy) in 590 controls and 1066 families with 1057 unaffected siblings and 1120 patients with nonaffective psychotic disorder, aged 16–50 years (Genetic et al., 2011). Both siblings and patients had significantly higher rates of cannabis use than controls. Furthermore, significantly more sibling cannabis users had clinical and subclinical psychotic symptoms than nonusers. But, there was no association between psychotic liability and cannabis use in the siblings. These findings led the GROUP to two conclusions. First, familial liability for psychosis increases susceptibility to the psychotomimetic effects of cannabis. Second, the tendency in siblings to use the drug reflects environmental not familial effects.

Several studies have examined if single-nucleotide polymorphisms (SNPs) play a role in the psychotomimetic effect of cannabis and in the risk for developing schizophrenia. Estrada et al. reported that the age at emergence of psychotic symptoms was significantly earlier among 80 Spanish adolescent psychotic inpatients who were Val/Val genotype carriers of catechol- O-methyltransferase (COMT) than among the Met carriers (Estrada et al., 2011). The Dunedin birth cohort study also demonstrated that carriers of the COMT Val158 allele were most likely to develop schizophrenia at age 26 if they had used cannabis during adolescence (Caspi et al., 2005). The Dutch GROUP reported that the SNP in AKT1 (rs2494732) not COMT moderated the short-term psychotomimetic effects of recent cannabis use and risk for psychotic disorder in 801 psychotic patients (van Winkel, 2011).

Summary and Conclusions

- Cannabis use in young adolescents can induce schizophrenia and is associated with increased illness severity.
- Earlier onset of schizophrenia in cannabis users is found in COMTVal158 carriers.
- Studies are needed to determine the role played by the interaction of familial loading for schizophrenia, demographic factors, childhood adversity, and early cannabis use in determining vulnerability or resilience for early-onset schizophrenia.

IMAGING OVERVIEW

In contrast to the previously described areas of research, a large number of imaging studies, in particular structural imaging studies, have been conducted on childhood and adolescent onset schizophrenia patients, their siblings, and typically developing youth. To help the reader understand the developmental implications of the imaging findings in schizophrenia, this section first describes the findings of structural imaging studies, magnetic resonance imaging (MRI), and diffusion tensor imaging (DTI) on normal brain development during childhood and adolescent.

It then reviews the findings of studies on global and regional cerebral gray and white matter cortical volume, cortical thickness, gyrification, white matter tracts, and subcortical structures in early-onset schizophrenia. A brief summary about the relationship of these findings to clinical symptoms and to functional impairment is provided for each of the reviewed brain structures and their associated networks. The imaging section concludes with a short description of the findings of functional imaging, connectivity, and graph theory studies in early-onset schizophrenia. Figure 21.1 orients the reader to regions of the lateral and superior surface of the cortex.

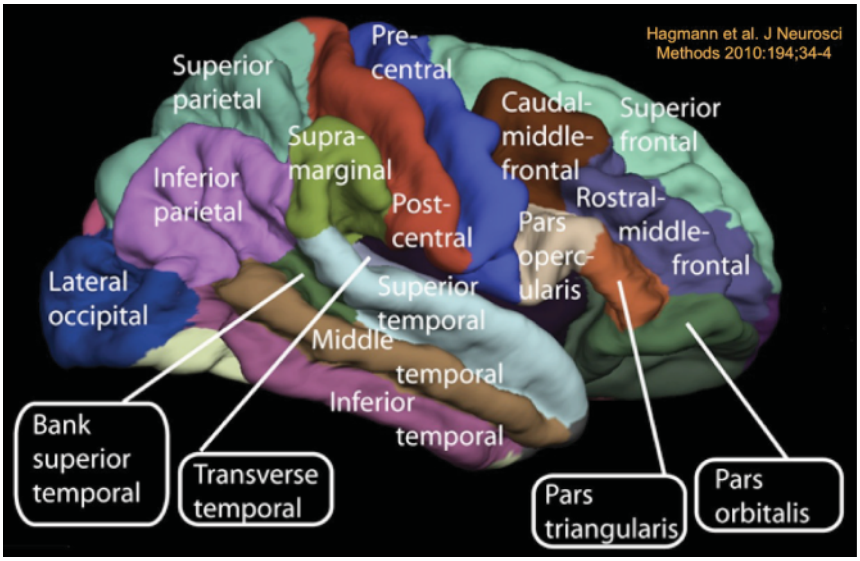


Figure 21.1 Lateral and superior surface cortical brain regions. See footnote 1. *Source:* Reprinted with permission from Hagmann, P., Cammoun, L., Gigandet, X., Gerhard, S., Ellen Grant, P., Wedeen, V., Meuli, R., Thiran, J.-P., et al. (2010). MR connectomics: Principles and challenges. *Journal of Neuroscience Methods, 194*(1), 34–45.

NORMAL BRAIN DEVELOPMENT

Gray Matter

Normal development of cortical volume, measured by manual drawings, voxel based morphometry (VBM), or Free Surfer (see review in Keller, 2009), has an inverted U–cubic trajectory with early accelerated increase followed by a progressive decrease during adolescence (Raznahan, Shaw, et al., 2011). It is a function of age- and gender-dependent change in cortical thickness and surface area, which in turn reflect growth of the external convex cortical area and gyrification and their relationship with age and gender. Later peaks in the cortical volumes of boys compared with girls are accounted for mainly by boys' faster and more sustained increase in surface area (Raznahan, Shaw, et al., 2011). These findings are based on more than 1250 prospective magnetic resonance imaging (MRI) scans of 647 typically developing subjects, aged 3–30 years.

The direction of change in cortical volume and thickness proceeds in a posterior to anterior direction (Sowell et al., 2004) with earlier peaks in the parietal lobe (girls: 10.2 years boys: 11.8 years), followed by the frontal (girls: 11.0 years, boys: 12.1 years) and temporal lobes (girls: 16.7 years, boys: 16.2 years) (Lenroot & Giedd, 2006) (Muftuler et al., 2011) (Figure 21.2). Of note, these brain regions include the heteromodal association cortex of the frontal, temporal, and parietal lobes that play an important role in higher-level integrative perceptual, cognitive, linguistic, and executive functions (attention, memory, planning, organization, emotional regulation, and social decision making). Thus, these higher order association and phylogenetically newer areas mature only after the lower order and phylogenetically older visual and somato-sensory regions (Gogtay et al., 2004).

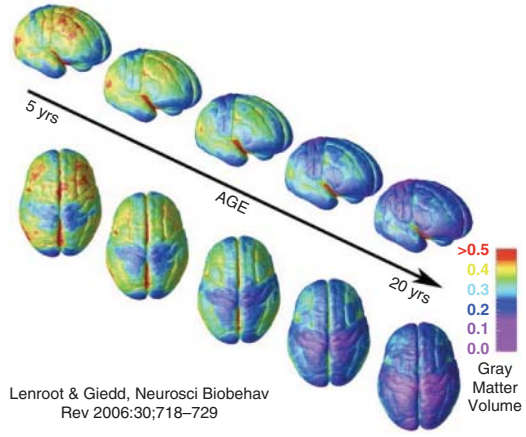


Figure 21.2 Right lateral and top views of the dynamic sequence of gray matter maturation over the cortical surface. The side bar shows a color representation in units of gray matter volume. Fifty-two scans from 13 subjects each scanned 4 times at approximately 2-year intervals. See footnote 1. *Source:* Reprinted with permission from R. Lenroot & J. Giedd, Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging, *Neuroscience and Biobehavioral Review, 30*(6), 718–729, 2006.

The ridges (convex curvature) of the brain are called gyri and the faults between them (concave curviture) are the sulci. The architecture of the gyri and sulci might play a role in connectivity and reflect plastic changes that occur as a result of pruning and environmental influences during development (see review in White, Su, Schmidt, Kao, & Sapiro, 2010). Gyrification, development of the folding surfaces of the brain is measured with the gyrification index, defined as the ratio between the lengths of coronal outlines for the brain including and excluding the sulcal regions (White et al., 2010). Depending on how the gyrification index is measured (for more details, see White et al., 2010), it is either constant from age 3 (Raznahan, Shaw, et al., 2011) or decreases with age in the left and right frontal, medial temporal lobes, and parietal and frontal lobes (Su, White, Schmidt, Kao, & Sapiro, 2013).

Normal maturation of the gray matter of subcortical structures occurs earlier than in the cortex with a more attenuated relationship with age (Brain Development Cooperative, 2012). There is an age-related increase in the volume of the thalamus (Brain Development Cooperative, 2012; Muftuler et al., 2011), amygdala, and hippocampus (Ostby et al., 2009), and a decrease in the volume of the caudate and globus pallidus (Brain Development Cooperative, 2012; Ostby et al., 2009). Findings are inconsistent regarding the cerebellum with some studies showing a decrease (Ostby et al., 2009) and others an increase through age 11 in cerebellar volume (Brain Development Cooperative, 2012). These subcortical structures are involved in sensory integration (thalamus), motor sequencing (caudate globus pallidus), memory (putamen, caudate, hippocampus, cerebellum), cognition and language (thalamus, cerebellum), facial recognition and empathy (thalamus), fear and anxiety (amygdala) (see reviews in (Behrens et al., 2003; D'Angelo & Casali, 2013; Middleton & Strick, 2000; Mullally & Maguire, 2014).

White Matter

Like gray matter volume, white matter volume is also measured using manual drawings, VBM, and Free Surfer of MRI scans. Diffusion tensor imaging (DTI) measures water diffusion displacement in neural fibres, such as nerve or brain white matter, and provides information on white matter integrity (see review in Beaulieu, 2002). The degree of water diffusion restriction or fractional anisotropy is sensitive to multiple biological processes including variation in the number and density of axonal membranes, myelination, and fiber organization.

Age related increase in white matter volume proceeds simultaneously in a more or less linear manner in the parietal, frontal, and temporal lobes based on 601 subjects, aged 3–25 years, who underwent 897 scans (Lenroot & Giedd, 2006). This process continues until age 25 years in the frontal and temporal lobes. The rate of change is steeper in boys than in girls (Lenroot & Giedd, 2006; Perrin et al., 2008) and boys have higher fractional anisotropy than girls in corticospinal, long-range association, and cortico-subcortical fibers (Herting, Maxwell, Irvine, & Nagel, 2012). Continuous and symmetric myelination of major fiber tracts that connect lower motor neurons, subcortical structures, such as the thalamus and basal ganglia, and occipital lobe with the frontal lobe, temporal with frontal lobes, the corpus callosum, and the cingulate begins in early childhood and continues through adolescence (Peters et al., 2012). As described for the gray matter volume changes, parallel maturation of children's cognitive, linguistic, executive function, and social skills imply an important role for these developmental changes in white matter volume and tracts.

Ventricles

Findings are inconsistent regarding age-related changes in the lateral ventricles. The previously described large prospective study by Lenroot et al. (Lenroot & Giedd, 2006) reported increased lateral ventricular volume with age in their 3–25 year old healthy subjects. Likewise, Ostby et al. (Ostby et al., 2009) demonstrated that an increase in age was associated with larger lateral ventricle volume in 171 subjects, aged 8–31 years divided into five age groups. The Brain Cooperative's smaller cross sectional study of 325 younger subjects, aged 4.5–18 years, did not confirm this relationship (Brain Development Cooperative, 2012). There appear to be no age effects for the volumes of the third and fourth ventricles (Ostby et al., 2009).

Asymmetry

The asymmetric distribution of cortical gray and white matter is stable across age with gray matter rightward asymmetry in the frontal and temporal lobes but leftward asymmetry in the occipital and parietal lobes (Brain Development Cooperative, 2012). There also is rightward asymmetry in the white matter of the temporal lobe but left asymmetry of frontal, parietal, and occipital lobe white matter. Although the subcortical structures including the lateral ventricle also have a leftward asymmetry, there is a rightward asymmetry in the putamen (Brain Development

Cooperative, 2012). In terms of gender effects, males have greater leftward asymmetry for gray matter in the parietal lobe and rightward asymmetry of the putamen compared with females (Brain Development Cooperative, 2012).

Summary and Conclusions

Gray Matter

- Cortical volume, thickness, and surface area increase during early childhood and gradually decrease from middle childhood through young adulthood in an anterior-posterior direction.
- Thalamic volume increases, volumes of caudate and putamen decrease, and findings are inconsistent regarding age-related changes in cerebellar volume.
- Volume of the lateral not the third and fourth ventricles increases with age.
- Parietal lobe, occipital lobe, thalamus, and lateral ventricle have leftward asymmetry and frontal lobe, temporal lobe, and putamen have rightward asymmetry.
- Gyrification index decreases with age in bilateral frontal, medial temporal and parietal lobe.

White Matter

- Myelination increases with age in cerebrum and major fiber tracts that connect lower and upper motor neurons and subcortical and cortical structures.
- Asymmetry is leftward for lobes other than the temporal lobe.

SCHIZOPHRENIA

Cerebrum: Global Structural Abnormalities

Gray Matter

Prospective studies conducted by the NIMH group on brain development in treatment resistant childhood and adolescent onset youth with schizophrenia and healthy controls provide important information on how schizophrenia impacts brain development. Thompson et al. (Thompson et al., 2001) investigated three dimensional maps of brain changes derived from repeat MRI scans over a 5-year period in 12 children with schizophrenia with a mean age of 13.9 years compared with 12 age and gender-matched healthy control subjects (Figure 21.3). They found significant between group differences in the previously described normal age-related cortical thinning. The children with schizophrenia had significantly more loss of gray matter than the control group.

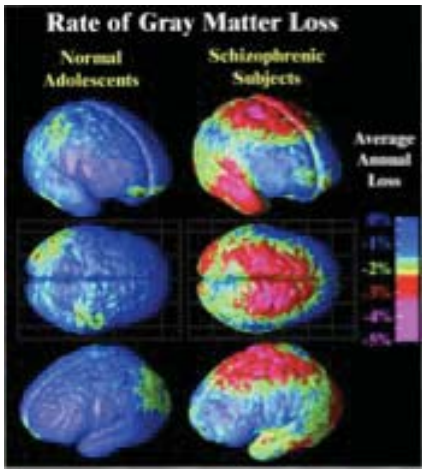
Earlier loss, evident in the parietal lobes, proceeded to the frontal cortex, then to the dorsolateral prefrontal cortex and finally to the temporal cortices in a back to front pattern. The dorsolateral prefrontal cortex and superior temporal gyrus were the last regions to undergo gray matter loss. This progressive spread over time involving the parietal, sensorimotor, supplementary motor, and temporal cortices did not include the inferior frontal lobe. A Spanish multisite Child and Adolescent First-Episode Psychosis Study (CAFEPS) of 61 children and adolescents with schizophrenia, aged 15.5 years, compared with 70 healthy controls also revealed a significant decrease in frontal lobe gray matter volume over time (Arango et al., 2012).

In contrast to adults with schizophrenia (see review in Fornito et al., 2009), involvement of the dorsolateral prefrontal lobe and frontal eye fields came late in the process. Comparison of the younger and older schizophrenia patients in the NIMH study demonstrated parietal involvement in the younger subjects but frontal involvement in the older subjects.

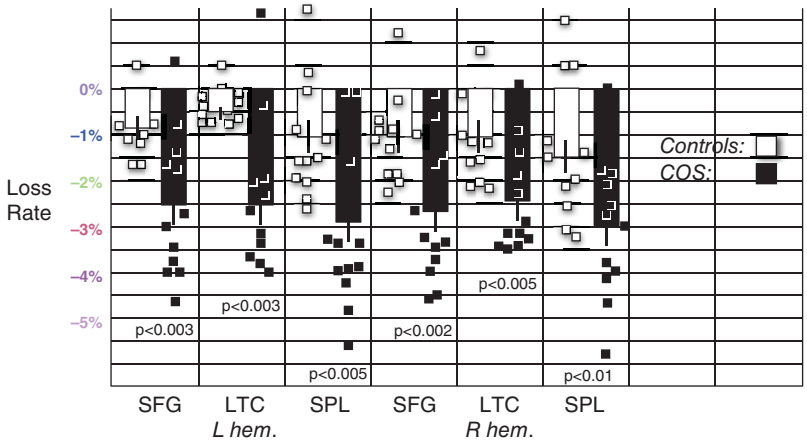
Highlighting the interaction between the neuropathology underlying the disorder and ongoing brain development, these findings suggest that the structural abnormalities in childhood onset schizophrenia evolve over time to resemble those of later onset schizophrenia. Thompson et al. concluded that cortical thinning in early-onset schizophrenia reflects illness rather than medication effects on brain development. This conclusion was based on similar, albeit less severe, cortical thinning patterns in children with psychosis NOS, who were matched on IQ and antipsychotic medication with the early-onset schizophrenia patients (Thompson et al., 2001).

Vidal et al. (Vidal et al., 2006) used the same approach to study dynamic changes in the medial hemisphere surface in early-onset schizophrenia, psychosis NOS, and control subjects. They found a left greater than right dorsal to ventral pattern of progressive gray matter loss that involved the superior medial frontal and precentral gyri of the frontal lobe as well as the cingulate. Medial limbic regions (hippocampus, parahippocampal gyrus), however, were uninvolved in this process. In terms of the time course, whereas the anterior medial frontal regions were involved throughout the study, progressive gray matter loss in the cingulate occurred late in the follow-up MRI scans. As for the lateral, superior, and inferior cortical regions studied in Thompsons et al. (2001), similar but attenuated findings in the psychosis NOS subjects supported the authors' conclusions that their findings did not reflect antipsychotic drug effects.

A cross sectional and prospective study of 49 NIMH early-onset schizophrenia subjects, mean age 14.7 years,



(a)



(b)

Figure 21.3 Average rates of gray matter loss in normal adolescents and in schizophrenia. (A) Three-dimensional maps of brain changes, derived from high-resolution magnetic resonance images (MRI scans) acquired repeatedly from the same subjects, reveal profound, progressive gray matter loss in schizophrenia (Right). Average rates of gray matter loss from 13 to 18 years of age are displayed on average cortical models for the group. Severe loss is observed (red and pink; up to 5% annually) in parietal, motor, and temporal cortices, whereas inferior frontal cortices remain stable (blue; 0–1% loss). Dynamic loss is also observed in the parietal cortices of normal adolescents, but at a much slower rate. (B) Average gray matter loss rates were computed for all 24 subjects in superior frontal gyri (SFG), lateral temporal cortices (LTC), and superior parietal lobules (SPL) in both brain hemispheres. Error bars indicate the standard error of the sample means, by region, in controls and patients. Individual loss rates (in percent per year) are plotted (■, patients; □, controls), showing significant group separation, despite some outliers. See footnote 1. *Source:* Reprinted with permission from P. M. Thompson, C. Vidal, J. N. Giedd, P. Gochman, J. Blumenthal, R. Nicolson, A. W. Toga, & J. L. Rapoport, Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia, *Proceedings of the National Academy of Sciences of the United States of America, 98*(20), 11650–11655, 2001. Copyright 2001 Naitonal Academy of Sciences, U.S.A.

found no differences between the patients and 50 age- and gender-matched healthy control subjects in cortical thickness asymmetry in both the lateral and medial cortical surfaces (Bakalar et al., 2009). However, Collinson et al. (Collinson et al., 2003) reported gender-related asymmetry difference in their cross sectional Oxford study of 33 early-onset schizophrenia subjects (mean age, 16.8, age of onset 15.7 years) relative to 30 age-matched controls (18 boys, 12 girls). The male patients ($N = 22$) had reduced leftward asymmetry and the female patients ($N = 11$) less rightward asymmetry compared with the control subjects.

Regarding gyrification, White et al. (White, Andreasen, Nopoulos, & Magnotta, 2003) reported that 42 youth with schizophrenia whose mean age was 17.7 years had significantly flattened curvature in frontal and parietal sulci but more steeped or peaked curvature in the occipital

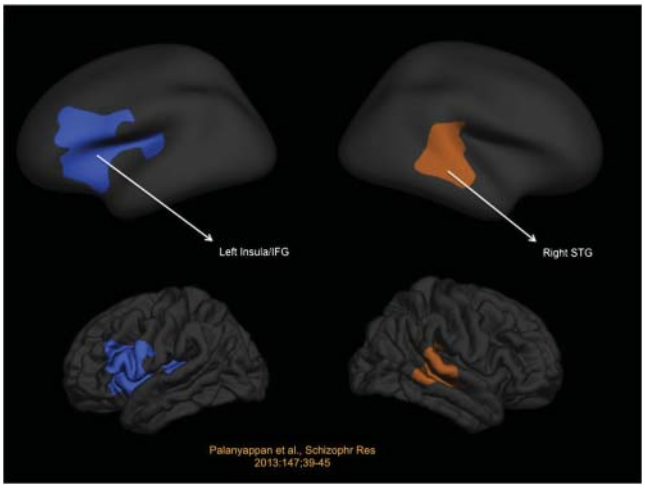


Figure 21.4 Clusters showing significant alterations in the gyrification index in adolescents with schizophrenia. Top panel: Clusters displayed on inflated average image (fsaverage). Bottom panel: Clusters displayed on the pial surface of the fsaverage image. Left hemisphere is shown on the left, right hemisphere is on the right. See footnote 1. *Source:* Palanyappan et al. Schizophr Res 2013: 147; 39–45.

gyri than 24 age- and gender-matched adolescents. Given current theories on the role of pruning in the formation and maturation of gyri and sulci (see review in White et al., 2010), these authors suggested that this finding might reflect illness-related abnormal cerebral and subcortical connectivity.

Supporting this theory, the amount of folded compared with unfolded cortex was increased in Broca's area (inferior frontal gyrus) extending to the interior insula and decreased in the superior temporal gyrus in Wernicke's area and the posterior insula in 18 early-onset schizophrenia subjects studied at Oxford compared with 19 controls, aged 13.5–17.8 years (Palaniyappan et al., 2013; Figure 21.4). In contrast to this left lateralized finding in the patients, gyrification in Broca's area and in the insula was right lateralized in the control group. Follow-up of these subjects over a two-year period demonstrated a significant reduction in gyrification in the patients but an increase in the controls. These authors suggested that early-onset schizophrenia might impact gyrification and sulcation during active pruning in brain regions involved in language (Broca's and Wernicke's areas) as well as in self-awareness and the ability to differentiate self from non-self (insula).

White Matter

Unlike the exaggerated and accelerated normal cortical thinning in children and adolescents with schizophrenia, the white matter growth rate of the 12 NIMH prospectively studied children with schizophrenia was significantly slower in the right hemisphere (frontal, temporal, parietal, and anterior cingulate) compared with healthy controls (Gogtay et al., 2008). In addition, it proceeded in a front to back direction in the patients with the greatest effect size in the right parietal lobe.

Thus, the patient group's baseline frontal lobe white matter volume was significantly smaller than that of the control group, and the between group differences became more evident in the posterior brain during the follow-up period. A cross sectional DTI study also reported significantly decreased white matter integrity in both parietal lobes of 19 early-onset schizophrenia youth, aged 13–19 years, compared with 20 age, gender, and socioeconomic-matched controls (Kyriakopoulos, Vyas, Barker, Chitnis, & Frangou, 2008).

Cerebrospinal Fluid

Since the brain is housed in a closed space, decreased gray and white matter volumes lead to expansion of cerebrospinal fluid and increased ventricular volume. Like the findings in adults with schizophrenia (Andreasen et al., 2011), two-year follow-up MRI scans of 39 early-onset schizophrenia patients from the NIMH study whose mean age was 14.5 years revealed a progressive increase in their lateral ventricle volume compared with 43 typically developing peers (Sporn et al., 2003).

Association with Clinical Symptoms, Cognition, and Premorbid Risk Factors

Clinical Symptoms. The previously described widespread gray (Thompson et al., 2001; Vidal et al., 2006) and white matter cortical abnormalities (Gogtay et al., 2008) in childhood onset schizophrenia were related to lower overall functioning. Worse severity of illness, reflected in duration of psychiatric hospitalization, also correlated with a significant reduction in frontal lobe gray matter volume in 61 children and adolescents with schizophrenia compared with 70 controls studied over two years in the CAFEPS (Arango et al., 2012).

Increased scores on the Scales for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1983), such as hallucinations, delusions, and loose associations, were associated with a higher rate of gray matter loss in the temporal lobe (mainly superior temporal gyrus) and medial surface of the frontal, parietal, and cingulate regions (Thompson et al., 2001; Vidal et al., 2006). Scores on the Scales for the Assessment of Negative Symptoms (SAPS) (Andreasen, 1983), including alogia, anhedonia,

and affective flattening, were related to frontal lobe gray matter loss (Thompson et al., 2001).

Cognition. The increased rate of gray matter loss (other than on the medial surface) (Thompson et al., 2001) and abnormal white matter development (Gogtay et al., 2008) were associated with lower IQ in the 12 NIMH schizophrenia patients. Baseline gray matter deficits also predicted lower follow-up IQ of these patients (Thompson et al., 2001). A cross sectional study demonstrated that smaller total gray matter volume in 52 early-onset schizophrenia subjects (18 with onset by age 13 and 36 with onset by age 18) compared with 48 healthy controls correlated with the patients' poor performance on executive, attention, verbal memory, motor, and sensory motor tasks (Kumra et al., 2011). The decrease in the gyrification index in the Oxford cohort of adolescents with schizophrenia followed for two years was related to impaired categorical fluency (the ability to list as many words as possible that are related to a specific category within a given time) (Palaniyappan et al., 2013).

Premorbid Risk Factors. Among the 60 NIMH childhood onset schizophrenia subjects followed every two years for 5–8 years, the children with more premorbid poor social interaction, delayed speech and language development, as well as motor problems that were evident more than one year before the onset of psychosis had a higher rate of gray matter loss than those with fewer premorbid problems (Sporn et al., 2003).

Summary and Conclusions

- Schizophrenia onset in childhood and adolescence impairs ongoing cerebral development with:
  - A progressive decrease in cortical gray matter volume and thickness — parietal → frontal → temporal lobe on the lateral and superior surface and — superior frontal lobe → cingulate on the medial surface.
  - An abnormal increase in white matter growth and volume, particularly in the right hemisphere.
  - A parallel increase in cerebrospinal fluid volume, mainly in the lateral ventricles.
- Temporal lobe and medial cortical surface gray matter loss and reduced white matter volume are associated with positive psychotic symptoms and poor overall functioning.
- Frontal lobe gray matter loss is related to negative symptoms and longer duration of illness.
- Lower IQ, extensive neuropsychological deficits, and premorbid social, speech/language, as well as motor difficulties are associated with gray matter loss and smaller volume.

Lobar, White Matter Tract, and Subcortical Structural Abnormalities

Structural abnormalities in the frontal, temporal, and parietal lobes, major white matter tracts, the corpus callosum, the cingulate, thalamus, hippocampus, basal ganglia, and cerebellum highlight the extensive brain damage and associated broad range of impairments involving cognition, language, emotions and affect, social skills, sensory, and motor functions in schizophrenia.

Lobar Abnormalities: Frontal Lobe

Frontal Lobe Function. Figure 21.1 describes the different parts of the frontal lobe. The prefrontal cortex is the association cortex of the frontal lobe that integrates a variety of information due to its extensive connections with other parts of the brain (Fuster, 2001). It includes the medial and orbital regions, involved in emotional behavior, as well as the lateral frontal lobe that "provides the cognitive support to the temporal organization of behavior, speech, and reasoning" (Fuster, 2001, p. 319). The level of complexity of processing by the frontal lobe appears to increase from the posterior to the anterior frontal pole and from ventral/lower to dorsal/upper frontal lobe areas (Fuster, 2001).

Connectivity of the orbital frontal area with the temporal pole, amygdala, and thalamus (Kubota, 2013) underlies its role in the regulation and control of social emotional functions. The connections of the lateral prefrontal cortex with the temporal, parietal, thalamus, cerebellum, and caudate subserve working memory, attention and other executive functions, including organization, planning, and monitoring (Fuster, 2001).

The inferior frontal gyrus includes the pars orbitalis, pars triangularis, and pars opercularis that are integrally involved in syntactical complexity, semantics, phonology, and speech production, respectively (Friederici, 2012) (Figure 21.1). These inferior frontal lobe regions are connected to the language-related regions in the temporal and parietal lobes through the long superior, middle, and inferior longitudinal fascicles and shorter arcuate and uncinate fascicles (white matter tracts) (Friederici, 2012) (Figure 21.5).

Through its connectivity with cortical and subcortical brain regions, the prefrontal lobe participates in the broad range of higher cognitive functions including perception, sensory-motor integration, language, cognition, and social behavior (Fuster, 2001). Two frontal lobe areas, the anterior cingulate and anterior medial prefrontal cortex, play a role in the initiation of motor acts (movement, speech), spontaneity, attention, and emotion (Fuster, 2001), in envisaging the perspectives of others (theory of mind) (see review

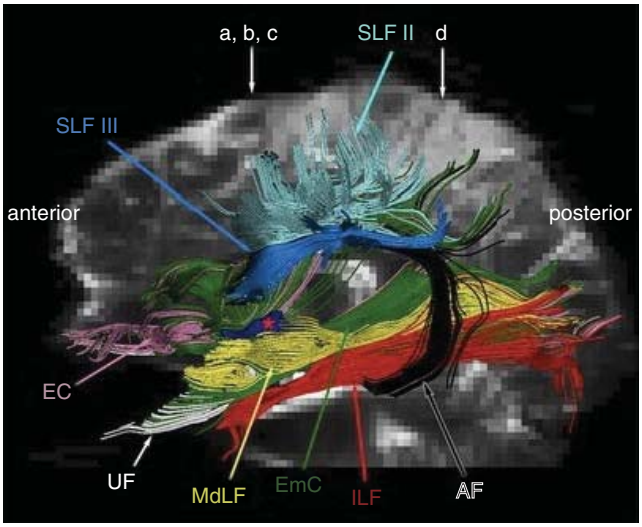


Figure 21.5 White Matter Tracts. SLF II and III = Superior longitudinal fascicle, ILF = Inferior longitudinal fascicle, MdLF = Middle longitudinal fascicle, UF = Uncinate fascicle, EC = External capsule. EMc = Extreme capsule. See footnote 1. *Source:* Springer and *Brain Structure and Function* 213(3), 2008, page, "The extreme capsule in humans and rethinking of the language circuitry," Makris and Pandya. Used with kind permission from Springer Science and Business Media.

in Frith & Frith, 2003), and in the ability to differentiate self from external sources (see review in Wang, Metzak, & Woodward, 2011). They also are part of the default mode network involved in internal processing thinking while at rest (Liu et al., 2013).

Schizophrenia. In terms of regional frontal lobe findings in early-onset schizophrenia, Kumra et al. (Kumra et al., 2011) reported significantly smaller superior frontal lobe gray matter volume in 52 youth aged 10–19 years with schizophrenia compared with 48 matched healthy controls. A smaller cross sectional study of 25 healthy controls and 25 adolescents with schizophrenia with onset between ages 11 and 15 years demonstrated gray and white matter volumetric and DTI abnormalities in the left inferior frontal lobe (Douaud et al., 2007). As previously mentioned, 25 adolescents, aged 14.2–18.4 years, had abnormal gyrification in Broca's area when compared with 25 control subjects (Palaniyappan et al., 2013).

Association with Clinical Symptoms and Cognition. Given the previously mentioned broad range of functions that the frontal lobe subserves, it is not surprising that a variety of psychotic symptoms are related to structural abnormalities in different parts of the frontal lobe. As evident from Table 21.7 on adult studies, the inferior frontal and medial and lateral orbital frontal regions are differentially involved in positive and negative psychotic symptoms,

TABLE 21.7 Symptoms, Cognition, and Frontal Lobe Regional Structural Abnormalities

Symptoms and Cognition	Regions	Reference
Positive		
Hallucinations	Anterior inferior frontal + connections with posterior temporal lobe	(Catani et al., 2011)
Formal thought disorder	Inferior frontal Orbital frontal	(Sans-Sansa et al., 2013)
Impaired insight Delusions of misattribution	Orbital frontal (pars orbitalis)	(Orfei, Piras, Macci, Caltagirone, & Spalletta, 2013)
Poor attribution of salience Reality distortion	Anterior cingulate	(Palaniyappan , Mallikarjun, Joseph, White, & Liddle, 2011)
Negative		
Flattened affect, anhedonia poverty of speech and of content of speech	Orbital frontal	(Sans-Sansa et al., 2013)
Cognition		
Memory decline	Orbital frontal	(Nestor et al., 2013)
Theory of mind	Ventromedial and ventrolateral prefrontal Anterior cingulate	(Hirao et al., 2008; Hooker, Bruce, Lincoln, Fisher, & Vinogradov, 2011)

poor insight and reality testing, misattribution of salience, memory decline, and poor theory of mind.

Only two early-onset schizophrenia studies have examined clinical variables associated with regional frontal lobe structural abnormalities. The U.K. Maudsley study of 40 early-onset schizophrenia youth with a mean age of 16.1 years, duration of illness of 14.1 months, and age of onset of 14.9 years reported that longer duration of illness was associated with smaller left inferior frontal gyrus volume (Burke, Androutsos, Jogia, Byrne, & Frangou, 2008). In addition, increased cortical thickness in the left orbitofrontal region predicted remission and possible response to treatment within 3 months of psychiatric admission for intractable schizophrenia in 16 of 40 NIMH patients (Greenstein, Wolfe, Gochman, Rapoport, & Gogtay, 2008).

Summary and Conclusions

- The frontal lobe integrates a variety of information relevant to behavior, cognition, language, and social skills due to extensive cortical and subcortical connections.
- In adult schizophrenia regional abnormalities in the orbital frontal, inferior frontal, superior and middle frontal lobe, dorsolateral prefrontal, and anterior cingulate regions are related to psychotic symptoms and cognitive impairment.

- In early-onset schizophrenia duration of illness and treatment response are associated with smaller inferior frontal and orbital frontal gray matter volumes.

Lobar Abnormalities: Temporal Lobe

Temporal Lobe Function. The left superior, middle, and inferior temporal gyri (Figure 21.1) are involved in the processing of language at the level of the word, the sentence, and the paragraph. They integrate language with other incoming sensory information (Friederici, 2011). In concert with their frontal and parietal connections they also participate in the bottom-up and top-down processing of language (see reviews in Friederici, 2011) and (Binney, Parker, & Lambon, 2012). The right temporal lobe plays a role in prosody (Friederici, 2011) coarse semantic coding during metaphor processing (see meta-analysis in Yang, 2012) in contrast to the fine semantic processing in the left language-related areas.

Maturation of children's complex syntactic and semantics skills depends on age-related development of dorsal and ventral white matter tracts that connect the superior temporal gyrus and inferior frontal gyrus (Figure 21.5) (Friederici, 2011). They allow the age-related top-down control of children's complex and abstract linguistic skills.

As part of its function as an association cortex, the temporal lobe is involved in the processing of different types of sensory stimuli and the integration of multimodal visual and auditory stimuli. Posterior to anterior longitudinal connectivity within the temporal lobe and horizontal connectivity across the superior, middle, and inferior temporal gyri play an important role in the complex integration of multimodal sensory functions involving visual and auditory perception (see review in Binney et al., 2012).

The tempero-parietal junction and superior temporal sulcus between the superior temporal gyrus and inferior frontal lobe, premotor cortex and sensory cortex (Figure 21.1) are part of a larger mentalizing network involved in the distinction between self and other and in affective theory of mind or the ability to place oneself in the affective state of another individual (see review in Shamay-Tsoory, 2012). The superior temporal sulcus is also sensitive to the presence of others and the interaction between them (Kujala, Carlson, & Hari, 2012). The anterior temporal lobe represents and retrieves social knowledge by using memory about people, their names and biographies, and more abstract forms of social memory such as memory for traits and social concepts (see review in Olson, McCoy, Klobusicky, & Ross, 2012).

Schizophrenia. Matsumoto et al. (2001) demonstrated significantly reduced right superior temporal gyrus gray matter volume in a stereological MRI study of 40 adolescents with schizophrenia, aged 15.5 years with a mean age of onset of 14.1 years, compared with 40 age, gender, socioeconomically matched healthy controls. Using VBM and tract based spatial statistics on white matter, Douad et al. (2007) also described gray and white matter abnormalities in Heschl's gyrus and in the temporal lobe of 25 adolescent onset schizophrenia patients compared with 25 typically developing adolescents studied at Oxford.

Furthermore, Palaniyappan et al. (2013) found decreased gyrification in the right superior temporal gyrus of these same 25 youth with schizophrenia. In a larger U.K. study Pentila et al. (2008) examined cortical folding in the temporal and collateral sulci (parahippocampal, fusiform, and lingual gyri) of 51 early-onset schizophrenia subjects with a mean age of 16 compared with 50 age and gender-matched healthy youth. The schizophrenia group had significantly lower bilateral global sulcal indices (the ratio between total sulcal area and total outer cortex area) and a lower sulcal index in the left collateral sulcus than the control groups. Bordering on medial temporal lobe structures (the hippocampus, fusiform gyrus, and lingual gyrus) involved in schizophrenia (Honea, Crow, Passingham, & Mackay, 2005), the collateral sulcus probably plays a role in the impaired memory (hippocampus), facial information processing (fusiform gyrus), and learning (lingual gyrus) found in patients with this illness.

Association with Clinical Symptoms and Social Cognition. Since the lateral temporal lobe is central to sensory integration and language, it is not surprising that it is involved in the abnormal auditory and visual perception (hallucinations), form of thought and speech (thought disorder), and thought content (delusions) of schizophrenia. In early-onset schizophrenia, positive signs on the SAPS of 29 youth with first episode psychosis (mean age 16.5 +/– 0.9 years), confirmed six months later as schizophrenia, had smaller left superior temporal gyrus and middle temporal gyrus volume than 34 healthy control subjects (Tang et al., 2012). The severity of both hallucinations and thought disorder were related to smaller right superior temporal gyrus volumes in the 40 adolescent patients described in Matsumoto et al. (2001). Of developmental interest, the youth with earlier onset had significantly smaller bilateral superior temporal gyrus gray matter volumes than those with later onset. Underscoring that onset of schizophrenia in younger

children is related to more severe brain abnormalities, this finding supports the neurodevelopmental theory of schizophrenia.

In terms of illness outcome, cortical thickness in the left superior temporal gyrus and left middle temporal gyrus was significantly higher in the 16 early-onset NIMH patients who remitted 3 months after treatment compared with the 40 patients with continued illness (Greenstein et al., 2008). Thus, youth with schizophrenia who undergo more normal cortical thinning during adolescence might have a better prognosis.

Summary and Conclusions

- The temporal lobe plays an important role in language, integration of multimodal visual and auditory information (relevant to perception and its disturbances), mentalizing, and social cognition (including theory of mind, emotional empathy).
- Youth with schizophrenia have reduced gray matter volume, thickness, and gyrification of the superior temporal gyrus, gray and white matter volumes of the Heschl's gyrus, and sulcal folding in the left collateral sulcus.
- Hallucinations, formal thought disorder, and poor treatment response are associated with these structural abnormalities.

Lobar Abnormalities: Parietal Lobe

Function. The parietal lobe subserves a wide range of functions including working memory, attention (sustained attention, alerting and shifting attention, inhibitory control of attention), retrieval of words and numbers, social cognition (theory of mind), as well as perceptual and motor orienting (see reviews in Cabeza, Ciaramelli, & Moscovitch, 2012; Criaud & Boulinguez, 2013). The mainly right-sided working memory and attention network includes the frontal lobe (dorsolateral prefrontal cortex, inferior frontal gyrus) and inferior parietal gyrus (Figure 21.1). The supramarginal gyrus and the region just behind it, the angular gyrus, are involved in word and number retrieval and the angular gyrus participates in reading.

The close connections of the parietal lobe with the sensory and visual cortex promote its role in perception and motor orienting (see review in Cabeza et al., 2012). The middle longitudinal fascicle is a white matter tract that connects the superior temporal gyrus to the superior and inferior (angular gyrus) parietal lobe (Asami et al., 2013) (Figure 21.5). Given its more ventral connections between the superior temporal gyrus and angular gyrus, this white tract is thought to play a role in language and attention. Its more superior connection between the superior temporal gyrus, superior parietal lobe, and occipital cortex probably participates the integration of visual-spatial audiovisual functions (Makris & Pandya, 2009) (Figure 21.5).

Schizophrenia. A Free Surfer study demonstrated significantly smaller left superior parietal gyrus gray matter volume and surface area in 35 early-onset schizophrenia patients, aged 10–12 years, compared with 51 healthy youth (Kumra et al., 2012). There have been no other studies to date on regional parietal structural abnormalities in early-onset schizophrenia patients compared with control subjects.

Association with Clinical Symptoms and Risk Factors. Among the 40 Maudsley early-onset schizophrenia subjects, aged 16.1 years, those with earlier age of onset (mean age of onset of 14.9 years and duration of illness of 14.1 months) had significantly smaller superior gray matter parietal volumes on the right (Burke et al., 2008). Cortical thickness in the bilateral postcentral and angular gyri was significantly higher in the 16 early-onset NIMH patients who remitted 3 months after treatment compared with the 40 patients with continued illness (Greenstein et al., 2008).

Cannabis use (see Risk Factor section) is related to regional reduction of parietal lobe gray matter volume. Comparison among 16 youth who were nonpsychotic cannabis users, 13 early-onset schizophrenia subjects who were also cannabis users, and 35 youth with schizophrenia revealed significantly smaller left superior parietal lobe gray matter volumes in each of these groups compared with 51 age-matched control subjects (Kumra et al., 2012). But there was no additive effect in the comorbid schizophrenia and cannabis use subgroup. Therefore, the authors of this study concluded that early-onset schizophrenia and cannabis independently increased the likelihood for this parietal lobe gray matter volume abnormality.

Summary and Conclusions

- Despite its role in sensory motor integration, perception, language, cognition, and social cognition, parietal lobe abnormalities in early-onset schizophrenia are understudied.
- Youth with schizophrenia, adolescent nonpsychotic cannabis users, and those with schizophrenia and cannabis use have decreased left superior parietal gyrus gray matter volume.
- Smaller right superior parietal gyrus gray matter volume is related to duration of illness.

- Treatment response is associated with smaller bilateral postcentral and angular gyri.

The Insula

Function. This brain region plays an important role in empathy and in awareness of the body's state (introception) through its perception of emotional, cognitive, and internal physical (i.e., visceral) stimuli (Wylie & Tregellas, 2010) (Figure 21.4). Of relevance to schizophrenia, the insula is involved in how one perceives one's own self-image and differentiates self from non-self and internal from external stimuli.

Schizophrenia. Moran et al. (2013) reported a significant reduction in both left and right insula volume in 98 NIMH early-onset schizophrenia patients compared with 100 healthy controls.

Association with Clinical Symptoms. Smaller right insula volume was significantly related to higher positive psychotic symptom scores and reduced left and right insula volume to poor overall functioning in these early-onset schizophrenia patients (Moran et al., 2013).

Summary and Conclusions

- Reduced bilateral insula volume and its role in differentiation between self and non-self appears to play a role in the positive psychotic symptoms and poor overall functioning of youth with schizophrenia.

Corpus Callosum

Function. The corpus callosum (Figure 21.6) is composed of nerve fibers of variable size that bridge between the hemispheres in a topographic manner so that anterior to posterior callosal fibres connect the left and right frontal, temporal, and parietal lobes and their respective motor, sensory, auditory, language, working memory, attention, and executive functions (see review in van der Knaap & van der Ham, 2011). There is an ongoing debate on whether the corpus callosum inhibits or excites the inter-hemispheric transfer of information because inhibition encourages lateralization whereas excitation leads to integrated bilateral function. Both inhibition and excitation might occur since functions, such as language, are lateralized whereas sensory functions, such as vision, are bilateral.

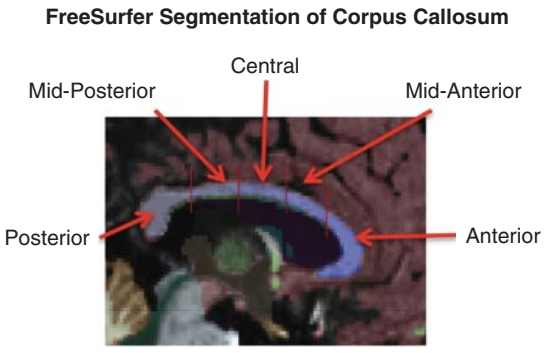


Figure 21.6 Subject MRI scan identifying the sub-regions of the corpus callosum. See footnote 1. *Source:* Reprinted with permission from S. L. M. Johnson, D. Greenstein, L. Clasen, R. Miller, F. Lalonde, J. Rapoport, & N. Gogtay, Absence of anatomic corpus callosal abnormalities in childhood-onset schizophrenia patients and healthy siblings, *Psychiatry Research, 20*(21), 11–16, 2013.

Schizophrenia. A prospective study of the volume of the corpus callosum in the NIMH childhood and adolescent onset schizophrenia patients ($N = 98$) found no significant differences compared with healthy controls ($N = 100$), aged 9–30 years (Johnson, Greenstein, et al., 2013). In contrast, cross sectional DTI studies of tract based spatial statistics on 25 (Douaud et al., 2007), 22 (White, Schmidt, & Karatekin, 2009), 15 (Davenport, Karatekin, White, & Lim, 2010), and 13 early-onset schizophrenia subjects (Henze et al., 2012) report significantly reduced white matter integrity in the genu (Figure 21.6) of the corpus callosum compared with the healthy control subjects. Despite the small sample sizes, similar impaired white matter integrity of the genu (anterior arched part) of the corpus callosum in these four studies might reflect the previously described impaired ongoing normal myelination of the frontal lobe during adolescence (Lenroot & Giedd, 2006).

Association with Clinical Symptoms and Cognition. There have been no studies to date on the relationship of corpus callosal structural abnormalities with symptoms and impaired cognition in early-onset schizophrenia.

Summary and Conclusions

- The corpus callosum, a major interhemisphere commisure, is involved in lateralization and bilateral integration of functions subserved by the frontal, temporal, and parietal lobes.
- There are no abnormalities in the gray matter volume and mid-sagital area of this brain structure in early-onset schizophrenia patients.
- Impaired white matter integrity of the genu that connects the left and right frontal lobes might reflect the impact of the disorder on the development of impaired executive function in youth with schizophrenia.

Hippocampus

Function. The hippocampus participates in remembering the past (memory), imagination (predicting the future), theory of mind (conceiving the viewpoint of others), and navigation (spatial orientation) (see reviews in Buckner & Carroll, 2007 and Mullally & Maguire, 2014). It is part of a core network that includes midline frontal structures, the frontal pole, and the medial temporal and parietal lobes (Buckner & Carroll, 2007). The skills subserved by the hippocampus mature through adolescence in parallel to ongoing development of the brain regions connected to the hippocampus.

Schizophrenia. Eighty-nine of the NIMH early-onset schizophrenia patients, aged 10–29 years, had significantly smaller bilateral hippocampal volumes compared with 79 matched healthy control subjects (Mattai A. et al., 2011). However, there was no significant difference in the longitudinal trajectory of hippocampal development in the patient and control group. A study on 103 NIMH patients and 101 controls identified shape abnormalities involving bilateral inward deformation of the anterior hippocampus (Johnson, Wang, et al., 2013).

Association with Clinical Symptoms. Decreased hippocampal volume in adults with schizophrenia is related to the severity of positive symptoms (Zierhut et al., 2013) but not in youth with this disorder (Mattai et al., 2011). However, bilateral inward deformation was significantly associated with the severity of positive psychotic symptoms and outward deformation with poor overall functioning (Johnson, Wang, et al., 2013).

Summary and Conclusions

- The hippocampus plays a central role in memory, imagination, spatial navigation, and theory of mind.
- Shape abnormalities but not reduced hippocampal volume are related to the clinical manifestations and poor functioning of youth with early-onset schizophrenia.

Thalamus

Function. This brain structure (Figure 21.7) is a relay station for pathways that connect all forms of sensory input, other than olfaction, from the periphery and the subcortical structures with the cortex (see review in Behrens et al., 2003). Table 21.8 and Figure 21.7 present diffusion imaging data based probabilistic tractography algorithm of thalamo-cortical connectivity (Behrens et al., 2003) and related functions (Jakab, Blanc, & Berényi, 2012; Llano, 2013; Watanabe & Funahashi, 2012).

TABLE 21.8 Thalamo-cortical connectivity and functions

Thalamic nuclei (n)	Cortical connectivity	Function
Mediodorsal n. Anterior n.	Prefrontal Temporal	Attention, working memory, verbal intelligence, naming
Lateral and inferior n. Posterior pulvinar	Temporal	Word, sentence generation, naming
Anterior pulvinar Lateral posterior n.	Posterior parietal Extra-striate	Reading
Ventral posterior lateral n.	Somatosensory	Sensations other than smell
Ventra lateral n. Ventral anterior n.	Motor Premotor	Movements

Schizophrenia. Compared with healthy youth, 46 psychotic boys under age 19, of whom 20 were diagnosed with schizophrenia spectrum diagnoses, had significantly smaller bilateral thalamic volumes involving mainly the right mediodorsal and pulvinar areas (Janssen et al., 2012). Two NIMH early-onset schizophrenia samples, one with 20 subjects (Frazier Jean et al., 2008) and one with 44 subjects (Kumra et al., 2000), demonstrated significantly smaller bilateral thalamus volume and reduced mid-sagital thalamic area, respectively, compared with typically developing children.

Association with Clinical Symptoms and Cognition. Although the abnormalities in the mediodorsal and pulvinar regions might contribute to positive psychotic symptoms and to executive function and linguistic deficits, the studies conducted to date in early-onset schizophrenia provide no information on these relationships. However, impaired sensory integration was related to smaller left and right anterior thalamus volumes and to earlier onset of psychosis in 40 first episode psychosis patients (Janssen et al., 2009).

Summary and Conclusions

- Thalamic nuclei participate in sensory integration, language, and cognition.
- Thalamic volumes, mainly mediodorsal nucleus and pulvinar, are reduced in schizophrenia youth.
- These volumetric abnormalities are associated with impaired sensory integration and earlier onset of the disorder.

Basal Ganglia: Caudate, Putamen, and Globus Pallidus

Function. The basal ganglia, together with the substantia nigra and subthalamic nucleus, are involved in movement,

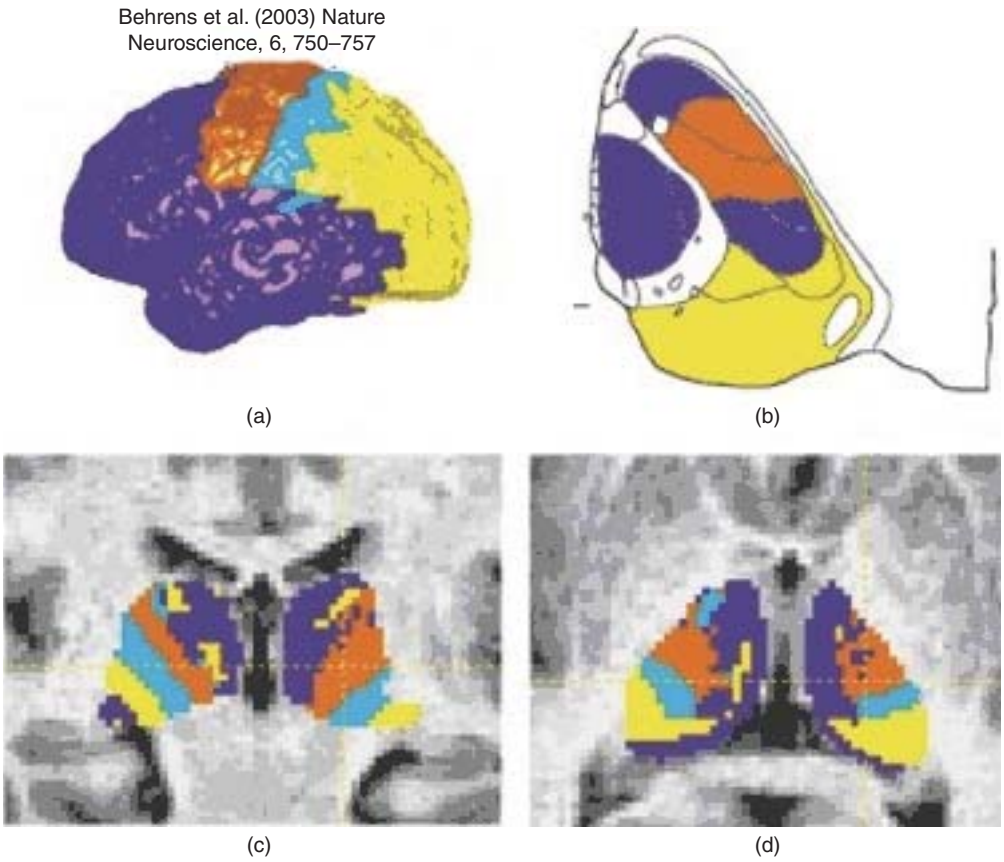


Figure 21.7 Connectivity-based segmentation of the thalamus in a single subject. (a) Division of the cerebral cortex according to anatomical landmarks (see Methods). (b) An axial section based on a histological atlas of the human thalamus with nuclei outlined by black lines. Nuclei have been color-coded according to the cortical zone to which we predict they would show the strongest connections, on the basis of data from nonhuman primates. (c,d) Classifying thalamic voxels based on the zone with the highest probability of connection resulted in clusters of commonly-connected voxels. The clusters correspond to histologically defined locations of major nuclei as in b. The medial, anterior purple area in c and d is thought to include the mediodorsal nucleus and nuclei within the anterior complex, which are connected to prefrontal cortex and the temporal lobe. The more posterior purple area is thought to include parts of the lateral and inferior pulvinar which connect to the temporal lobe. The yellow area is thought to include the anterior pulvinar and the lateral posterior nucleus which project mainly to posterior parietal and extrastriate areas. The blue area is thought to include the ventral posterior lateral nucleus, which projects to somatosensory cortices. The orange area is thought to include the ventral lateral and ventral anterior nuclei, which project to motor and premotor cortices. See footnote 1. *Source:* Reprinted by permission from Behrens, T., Johansen-Berg, H., Woolrich M.W., Smith S.M., Wheeler-Kingshott C.A., Boulby P.A., Barker GJ, Sillery EL, et al. Behrens, T., Johansen-Berg, H., Woolrich M.W., Smith S.M., Wheeler-Kingshott C.A., Boulby P.A., Barker GJ, Sillery EL, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging, *Nature Neuroscience, 6*(7), 750–757, 2003.

cognition, sensory functions, and behavior (see review in Middleton & Strick, 2000).

Schizophrenia. Only two studies report caudate, putamen, and globus pallidus volumes in early-onset schizophrenia compared with typically developing control subjects. An early NIMH study on 21 patients (of whom 12 had onset before age 12 years) demonstrated significantly larger caudate, putamen, and globus pallidus gray matter volumes than 33 healthy control subjects (Frazier et al., 1996). A two-year follow-up of 18 of these patients treated with clozapine showed normalization of these caudate volumes. Juuhl-Langseth et al. (2012) also reported a bilateral enlargement of caudate volumes in 18 early-onset schizophrenia subjects compared with 33 healthy control subjects. However, these authors examined a large number of subcortical volumes, 29, in a small sample of subjects, and 13 of the 18 patients were on a variety of antipsychotic drugs.

Association with Clinical Symptoms. In light of the small sample size of the above child studies, it remains to be determined if antipsychotic drugs increase caudate volume in early-onset schizophrenia. Tremor, dyskinesias, and

rigidity can occur due to treatment with antipsychotic drugs (see review in Walther & Strik, 2012). However, there is a wide range of motor abnormalities in schizophrenia, including early developmental delay and poor coordination (see Risk Factor section), tremor, chorea, dyskinesia, and slowing that are apparent at diagnosis (Biswas, Malhotra, Malhotra, & Gupta, 2007). These movement abnormalities are also found in children with putative antecedents of schizophrenia (MacManus et al., 2012).

Although these movement symptoms suggest involvement of frontal and striatal dopamine circuits, few studies have examined if they are associated with structural abnormalities in early-onset schizophrenia. Janssen et al.'s 70 adolescents with first episode psychosis and diagnosis of schizophrenia at the 6-month follow-up showed a significant association between smaller right caudate volumes and impaired complex motor sequencing (Janssen et al., 2009).

Summary and Conclusions

- The basal ganglia play a prominent role in movement.
- Youth with schizophrenia have transient enlarged caudate volumes that might represent a medication effect.
- Despite the wide range of motor abnormalities in schizophrenia, few studies have examined the relationship frontostriatal structural abnormalities in these patients.

Cerebellum

Function. Through its connections with the entire brain, the cerebellum (Figure 21.8) plays a role in sensory-motor coordination, sequence learning, attention, processing speed, visual-spatial function, language, and emotions

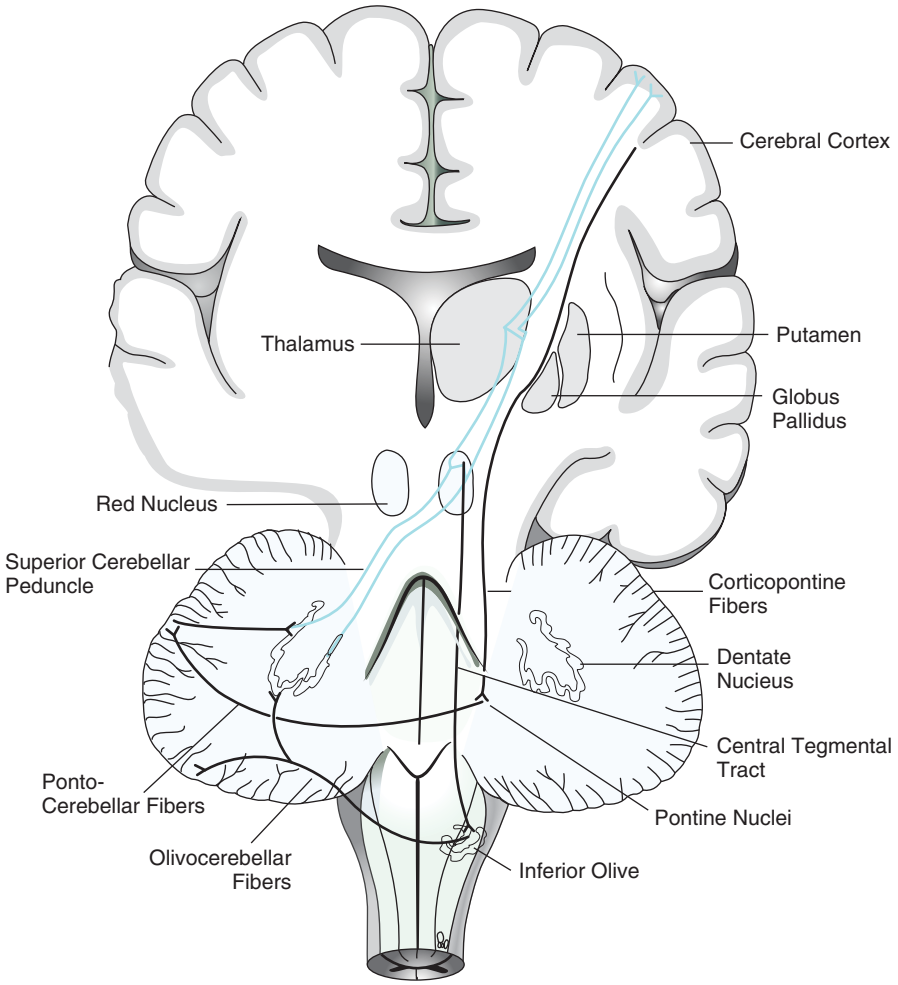


Figure 21.8 Cortico-cerebellar-thalamic-cortical circuit. See footnote 1. *Source:* Reprinted with permission from N. C. Andreasen & R. Pierson, The role of the cerebellum in schizophrenia, *Biological Psychiatry, 64*(2), 81–88, 2008.

(see reviews in D'Angelo & Casali, 2013) and (Andreasen & Pierson, 2008). Cerebellar anatomy is organized to permit it to perform fine-tuned pattern perception, error detection, and rapid online modulation and coordination (Andreasen & Pierson, 2008). D'Angelo and Casali argue that the cerebellum operates as a general-purpose co-processor, whose effects depend on the specific brain centers to which individual modules are connected. They suggest that normal and abnormal functioning in these neural loops could eventually contribute to the broad range of functions subserved by the cerebellum and to the pathogenesis of neuropsychiatric disorders including schizophrenia, dyslexia, autism, and depression.

Schizophrenia. A cross section of 94 early-onset schizophrenia patients from the NIMH sample demonstrated significantly smaller bilateral anterior cerebellar lobe volumes as well as reduced anterior and total vermis volumes compared with 100 control subjects (Greenstein et al., 2011). The patients' developmental trajectory diverged from that of the control group. They continued to have significantly smaller total and left and right hemisphere cerebellar volumes as well as decreased bilateral posterior inferior cerebellar volumes in the control group.

Association with Clinical Symptoms and Cognition. Andreasen (Andreasen & Pierson, 2008) coined the term cognitive dysmetria to capture the broad range of symptoms in schizophrenia (perception, language, concept formation, volition, social behavior, movement, attention, memory, emotion); the difficulty these patients have coordinating the processing, prioritization, retrieval, and expression of information; and the anatomical substrates of dysmetria (the motor cortex and its subcortical connection to the cerebellum via the pons, thalamus, and basal ganglia). For more detail on how this might reflect the specific micro-architecture of the cerebellum, see D'Angelo and Casali (2013) and Andreasen and Pierson (2008).

Andreasen and Pierson suggested that symptoms, such as hallucinations and delusions result when "... pattern and error detection tasks normally performed by the cerebellum are presumed to respond in a flawed manner in patients suffering from schizophrenia. Instead of modulating and coordinating, they misconnect the billions of pieces of information arriving from the cerebral cortex" (Andreasen & Pierson, 2008, p. 82). Nevertheless, most structural MRI researchers on schizophrenia have neglected the humble cerebellum (Andreasen & Pierson, 2008) and cerebellar structural findings are inconsistent (see review in Greenstein et al., 2011).

As found in other neuropsychiatric disorders, the NIMH cross sectional but not the prospective study demonstrated an association between IQ and vermal volume (see review in Greenstein et al., 2011). Reduced volume of the vermis also correlated with poor overall functioning at baseline but not over time. Furthermore, the baseline and developmental trajectory cerebellar abnormalities in these youth were unrelated to psychotic symptoms.

Summary and Conclusions

- The cerebellum acts as a general-purpose co-processor for the fine-tuning of sensory-motor coordination, sequence learning, attention, processing speed, visual-spatial function, language, and emotions.
- When studied cross sectionally, youth with schizophrenia have statistically smaller anterior cerebellar lobes, as well as anterior and total vermal volumes but reduced total, right and left cerebellar hemisphere, and bilateral posterior inferior cerebellar volumes when studied longitudinally.
- The relationship of abnormal vermal volumes with IQ and poor overall functioning is transient in these patients.
- Psychotic symptoms are also unrelated to cerebellar volume abnormalities.

Family and Clinical Risk for Schizophrenia

Family High-Risk

A cross sectional study demonstrated significantly reduced left prefrontal and bilateral temporal gray matter in 52 siblings (aged 8–28 years) of the large NIMH early-onset schizophrenia cohort compared with 52 control subjects (Gogtay et al., 2007). Mattai et al. (2011) replicated these findings in an additional NIMH cohort of 43 siblings, aged 5–26 years, and 86 control subjects. Of note, longitudinal follow-up of gray matter thickness in both sibling samples showed normalization of these findings by age 20 and 17 in the Gogtay et al. and Mattai et al. studies, respectively. Similarly, a 5-year follow-up of white matter growth in 49 siblings of the schizophrenia subjects (mean age 16.1 years) identified slower growth only in the younger group of 7–14 year old siblings (Gogtay et al., 2012).

In contrast to adult sibling and offspring studies (Francis et al., 2011; Palaniyappan, Balain, & Liddle, 2013), the NIMH sibling cohort also did not demonstrate structural abnormalities in the insula (Moran et al., 2013), corpus callosum (Johnson, Greenstein, et al., 2013), hippocampus (Johnson, Wang, et al.; Mattai et al., 2011), and cerebellum

(Greenstein et al., 2011). Developmental, methodological, and illness severity variables in the child and adult studies might underlie these different findings. Among other factors, the methodological differences include the type of morphometric variable studied (volume, cortical thickness), their measurement (MRI scanner and data reduction using manual drawing, VBM, or FreeSurfer), the study design (cross sectional versus prospective studies), heterogeneity of study probands (inclusion of subjects who also have nonpsychotic diagnoses), and lack of matching on demographic variables (ethnicity and socioeconomic status). The NIMH researchers also noted that the normalization of sibling findings might reflect the fact that the brains of a large number of the siblings in their studies were still undergoing development and that many of the siblings were within the age of risk for schizophrenia (Greenstein et al., 2011).

Clinical High-Risk

Among 75 individuals, aged 14–30 years, with prodromal signs of psychosis, the 23 who developed psychosis within 12 months (8 with one of the schizophrenia spectrum diagnoses) had less gray matter at baseline in the right medial temporal, lateral temporal, inferior frontal cortex, and bilateral cingulate cortex than those who did not develop psychosis (Pantelis et al., 2003). Repeat scans at the 12-month follow-up of 21 high-risk subjects demonstrated a significant reduction in gray matter in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, as well as the cingulate gyri in the 10 who became psychotic (5 with schizophrenia) (Pantelis et al., 2003). These findings further support the role of frontotemporal regions including the cingulate in the clinical risk and conversion to psychosis.

A comparison of gray and white matter volumes in 20 children with putative signs of psychosis and 20 matched healthy controls, aged 9–12 years, found decreased gray matter volumes in the right middle temporal gyrus, increased gray matter volume in the left superior-middle temporal gyri, and larger white matter volume the left superior temporal gyrus, inferior parietal lobe, and occipital lobe (Cullen et al., 2013). Involvement of the parietal and occipital lobe in the young children in this study might reflect the impact their being at risk for adult onset schizophrenia on the ongoing cortical thinning in posterior brain regions. As previously explained, the NIMH findings for schizophrenia subjects with childhood versus adolescent onset demonstrated reduced gray matter in the parietal lobe only in the childhood onset subjects (Gogtay, 2008).

Summary and Conclusions

- Imaging findings in individuals at genetic and clinical risk for schizophrenia provide important information on resilience and risk for the disease.
- Resilience for early-onset schizophrenia in siblings includes normalization by age 17–20 of frontotemporal gray matter reduction and slow white matter growth, as well as no structural abnormalities in the insula, corpus callosum, hippocampus, and cerebellum.
- Resilience among individuals at clinical risk for schizophrenia is related to normal frontotemporal and cingulate gray matter thickness/volume.

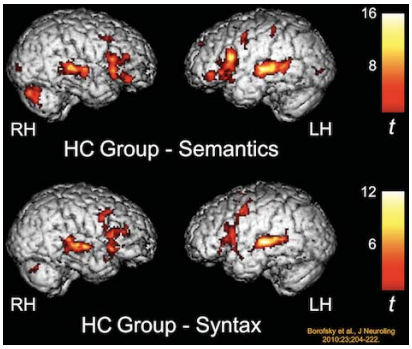
Functional Imaging Studies

The few functional imaging studies that have been conducted in early-onset schizophrenia have focused mainly on language (Borofsky et al., 2010), memory (Kyriakopoulos et al., 2012; White, Hongwanishkul, & Schmidt, 2011), and visual processing (White, Moeller, Schmidt, Pardo, & Olman, 2012).

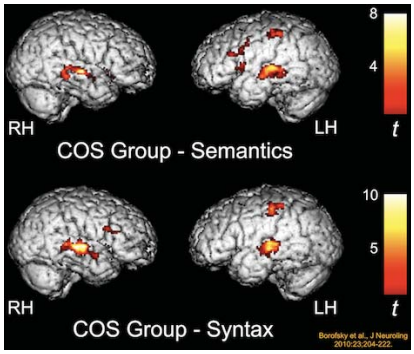
Language and Formal Thought Disorder

Children with schizophrenia (N = 14, mean age: 13.34; IQ: 95) and healthy controls (N = 14, mean age: 12.37; IQ: 104) underwent functional MRI (fMRI) during a semantic judgment task previously shown to differentially engage semantic and syntactic processes (Borofsky et al., 2010). Despite similar performance on the tasks in both groups, the schizophrenia group had increased right lateralization of neural activity during the syntactic condition as found in adults with schizophrenia (see review in Rapp & Steinhäuser, 2013). Different patterns of functional specialization for semantic and syntactic processing in the children with schizophrenia compared with the control group suggested that the patients code semantic and syntactic information differently than the healthy children (see Figure 21.9).

In the patient group formal thought disorder was significantly related to decreased cortical activity during the semantic condition in the left superior temporal gyrus, dorsolateral prefrontal gyrus, dorsomedial frontal gyrus, and inferior frontal gyrus. Formal thought disorder was also associated with reduced neural activity during the syntactic condition in the left inferior frontal gyrus and superior temporal gyrus as well as the insula. These findings corroborate the previously described structural abnormalities in language-related regions in early-onset schizophrenia.



(a)



(b)

Figure 21.9 Cortical activity during semantic and syntactic task in Healthy Control (HC) and Childhood Onset Schizophrenia Groups (COS). a. Several clusters of significant activity in frontotemporal language regions were observed in HC children for both the semantic (top) and syntactic (bottom) conditions as compared with resting baseline. Activation maps are displayed at a threshold of $t > 3.85$, $p < 0.001$ for magnitude, $p < .05$, corrected for spatial extent. b. Children with COS also showed significant task-related activity during the semantic (top) and syntactic (bottom) conditions as compared with resting baseline, albeit to a lesser degree than observed in the HC group. Activation maps are displayed at a threshold of $t > 3.85$, $p < 0.001$ for magnitude, $p < .05$, corrected for spatial extent. See footnote 1. *Source:* Reprinted with permission from L. A. Borofsky, K. McNealy, P. Siddarth, K. N. Wu, M. Dapretto, & R. Caplan, Semantic processing and thought disorder in childhood-onset schizophrenia: Insights from fMRI, *Journal of Neurolinguistics, 23*(3), 204–222, 2010.

Cognitive Processing

Twenty-five youth with schizophrenia, aged 12–19 years and illness onset before age 18, showed significantly reduced activation in the dorsolateral prefrontal cortex, the anterior cingulate, and the frontal operculum during a 2 N back working memory task compared with 20 age-matched control subjects (Kyriakopoulos et al., 2012). The patient group also had reduction in the coupling of the dorsolateral prefrontal cortex, the anterior cingulate, the parietal cortex, and the middle occipital gyrus. Whereas the control group showed an age-related increase in activity in the dorsolateral prefrontal cortex and a decrease in its connectivity with the anterior cingulate cortex during this task, the opposite was found in the patient group. The authors concluded that early-onset schizophrenia is associated with dysfunctional neural engagement of the working memory network and integration of its components.

During a visual spatial working memory task with three different loads, White et al. (2011) reported increased activation in the anterior cingulate, insula, medial temporal lobe, and bilateral lateral temporal lobes in 22 subjects with schizophrenia (mean age was 15.7 years) compared with 24 age-matched controls. With increasing memory load, the patients demonstrated less activation in the parietal lobe compared with the control group. The authors concluded that lack of involvement of the prefrontal cortex function in the working memory task might reflect the developmental impact of the disorder. Their findings support limbic, temporal lobe, and parietal lobe abnormalities during visual spatial working memory.

Multimodal imaging in 11–13 year old children with subclinical symptoms of psychosis ($N = 11$) demonstrated aberrant prefrontal-temporal function in addition to cingulate and insular dysfunctions during a task of response inhibition and error-related processing, respectively, compared with 14 age-matched control subjects (Jacobson et al., 2010). Interestingly, 19 adolescent offspring of parents with schizophrenia also demonstrated dysfunction in frontostriatal pathways and inefficient cognitive processing during a visual working memory task compared with 25 healthy control subjects (Diwadkar et al., 2012). Despite similar performance on the task in both groups, the offspring showed increased activation of the dorsal prefrontal cortex and the caudate during correct compared with incorrect responses. In the control group, however, task proficiency was associated with activation in the caudate.

Summary and Conclusions

- Children with schizophrenia have right lateralization during a semantic task and different activation patterns than healthy control subjects when processing a semantic and a syntactic task.
- Formal thought disorder in children with schizophrenia is associated with decreased activity in language-related regions during a semantic and a syntactic task.
- Decreased cortical activity during working memory tasks identifies dysfunctional neural engagement and integration of the components of the working memory network in youth with schizophrenia.

Connectivity and Graph Theory

One of the main breakthroughs of the imaging studies conducted over the past decade is the identification of connectivity networks, the functions they subserve, and their abnormalities (disconnection) in schizophrenia (see review in Yu et al., 2012). A recent functional connectivity study at rest in 20 healthy adults and 20 age-matched patients who had childhood onset schizophrenia found reduced strength of functional connectivity over short distances localized specifically to connector hubs of multimodal association cortex (Alexander-Bloch et al., 2013). The authors of this study suggest that spatial and topological disturbances of functional network organization could arise from excessive pruning of short-distance functional connections in these patients.

Imaging studies over the past decade have also led to identification of the default mode network or brain regions that are active at rest including the precuneus, anterior and posterior cingulate, medial prefrontal cortex, parahippocampus, and inferior parietal cortices. Tang et al. (2012) described decreased functional connectivity between the medial frontal gyrus and other regions of the default mode network in 32 schizophrenia patients, aged 12–19 years, with recent onset (mean 9.8 months) compared with 38 matched healthy control subjects. They concluded that their findings might reflect abnormal introspective mental activity.

Summary and Conclusions

- Application of graph theory to connectivity studies suggests there is reduced connectivity over short distances in hubs connected to the multimodal association areas in early-onset schizophrenia.
- Impaired connectivity in the default network of youth with schizophrenia might reflect abnormal introspective mental activity.

GENETICS

Genomic studies have shown that schizophrenia is a genetically heterogeneous disorder involving different cytogenetic abnormalities and genetic loci (see review in (McClellan & King, 2010). Rare copy number variants (CNVs) disrupt genes involved in glutamate and neuroreglin pathways and in signaling, synaptic plasticity, and neurodevelopmental processes (McClellan & King, 2010). CNVs that occur de novo are 8 times more common in patients whose illness is not familial (McClellan & King, 2010). But CNVs and other structural genetic abnormalities might also be unique to individual families (McClellan & King, 2010).

Although rare, some CNVs occur at genetic hot spots on chromosomes 1q21.1, 3q29, 15q11.2, 15q13.1, 16p11.2, and 22q11.2 (McClellan & King, 2010). In early-onset schizophrenia they also involve chromosomes 2p16.3 (NRXN1), 15q13.3, 16p13.1, and 17p12 (Ahn et al., 2013). There is a higher rate of rare structural variants and large cytogenetic abnormalities in early-onset compared with adolescent and adult onset schizophrenia (Addington & Rapoport, 2009; Ahn et al., 2013).

Compared with 69 siblings, significantly more childhood onset schizophrenia patients in the NIMH cohort (N = 126) had CNVs with a total of 46 rare CNVs (Ahn et al., 2013). Fifteen patients in this cohort had at least one CNV on chromosomes 22q11, 8q11.2, 10q22.3, 16p11.2 and 17q21.3.

Some of the structural imaging findings found in early-onset schizophrenia are associated with susceptibility genes for schizophrenia. Raznahan et al. (2011) found that among 82 youth with schizophrenia and their 62 siblings (aged 9–22 years), those with the Valline not the Methionine allele of COMT located on chromosome 22 had accelerated dorsolateral prefrontal cortical thinning compared with the attenuated thinning found in the 208 healthy controls. These findings suggest that the reduced cortical thickness found in early-onset patients with schizophrenia might reflect genetic effects. In addition, since the association between accelerated cortical thinning and the Val allele in the siblings normalized over time, Raznahan et al. concluded that the patients' morphometric findings were unrelated to antipsychotic drug treatment.

Most recently in an elegant three stage study of 105 probands with schizophrenia and 84 unaffected siblings, Gulsuner et al. (2013) showed that a network of proteins involved in de novo mutations in probands but not in their siblings is active during fetal development in the dorsolateral prefrontal and ventrolateral frontal lobe. These proteins are "critical to neurogenesis and synaptic integrity, including axon guidance and neuronal migration, signaling, cell proliferation, transport, synaptic transmission, and transcriptional regulation." These findings support the role of the frontal lobe in the neurodevelopmental theory of schizophrenia proposed by Weinberger (Weinberger, 1987).

Among the genetic hot spots for schizophrenia, the microdeletion of 40 genes in and around q11.2 of chromosome 22 is associated with adult onset of a schizophrenia-like psychosis and schizotypal traits in about one-third of youth with this genetic abnormality (Green

et al., 2009). In fact, other than having two parents with schizophrenia, this syndrome is the highest genetic risk factor for schizophrenia (Bassett, Chow, O'Neill, & Brzustowicz, 2001). Additional psychiatric diagnoses found in this syndrome include autism, obsessive-compulsive disorder, phobias, ADHD, generalized anxiety disorder, and depression (see review in Sinderberry et al., 2013). It is also associated with cardiac (De George Syndrome) and palatal abnormalities (velo-cardiac syndrome), as well as impaired cognition (IQ, verbal memory, and executive function).

A large prospective study on brain volumes demonstrated that subjects with 22q11 who exhibited prodromal symptoms at the 3-year follow-up had significantly smaller cranial gray and white matter, prefrontal cortex, mesial temporal lobe, and cerebellar volumes (Kates et al., 2011). The presence of positive symptoms of psychosis was associated with a significant decrease over time in temporal lobe gray matter volume and in verbal IQ. Reduction in temporal lobe gray matter and in verbal IQ also predicts conversion to schizophrenia in youth with clinical risk for schizophrenia (Pantelis et al., 2003; Takahashi et al., 2009), first episode psychosis (Tang et al., 2012), and putative antecedents of schizophrenia (Cullen et al., 2013).

Finally, individuals with autism, intellectual disability, and epilepsy have similar cytogenetic abnormalities similar to patients with schizophrenia that occur on 1q21.1, 15q13.3, 22q11.2, 15q11-q13, and 16q11.2 (McClellan & King, 2010). Mutations disrupting *NRXN1*, *SHANK3*, *CNTNAP2*, and *PRODH* are associated with both schizophrenia and autism (McClellan & King, 2010). Recent clinical evidence for a two-way relationship of epilepsy with schizophrenia (Adelöw, Andersson, Ahlbom, & Tomson, 2012; Hesdorffer et al., 2012; Qin, Xu, Laursen, Vestergaard, & Mortensen, 2005) support these genetic findings. Furthermore, evidence for a critical period during which patients with schizophrenia are more likely to develop epilepsy and epilepsy patients are at increased risk for being diagnosed with schizophrenia (Adelöw et al., 2012; Hesdorffer et al., 2012), underscores the importance of examining the possible role of psychosocial environmental variables.

Finally, although environmental factors play a role in schizophrenia, when and why disruption of the balance between environmental and genetic factors results in the illness remains to be elucidated. In fact, there is a dearth of studies on the role of psychosocial factors in early-onset schizophrenia.

Summary and Conclusions

- Rare copy number variants and de novo mutations occur x8 higher in nonfamilial schizophrenia.
- The offspring of two parents with schizophrenia and probands with chromosome 22q11 mutation have the highest risk for the disorder.
- Childhood onset of schizophrenia is associated with more CNVs than adolescent onset of the disorder.
- Genetic hot spots for the disorder are found on chromosomes 1q21.1, 3q29, 15q11.2, 15q13.1, 16p11.2, and 22q11.2.
- Similar cytogenetic abnormalities are found in schizophrenia, autism, intellectual disability, and epilepsy. Studies are warranted to determine how environmental psychosocial factors trigger the onset of schizophrenia in genetically predisposed youth.

TREATMENT

Antipsychotic Drugs

Typical neuroleptics or first-generation antipsychotic drugs with US Federal Drug Administration (FDA) approval to treat 13–17-year-old schizophrenia youth include haloperidol, chlorpromazine, thioridazine, molindone (now no longer available), and thiothixene (see review in Carlisle & McClellan, 2011). Although effective for positive symptoms of schizophrenia (e.g., hallucinations, delusions, disorganized behavior), lack of efficacy for negative symptoms and induction of extrapyramidal symptoms (EPS) (rigidity, tremor, akathisia), tardive dyskinesia (i.e., involuntary oral-buccal-lingual masticatory movements), and weight gain have limited their use in children.

Based on efficacy and safety findings in double-blind randomized controlled studies, the FDA approved atypical neuroleptics or second-generation antipsychotic drugs including risperidone (1–3mg/d or 4–6mg/d), (Haas et al., 2009), olanzepine (2.5–20.0 mg/d) (Kryzhanovskaya et al., 2009), and aripiprazole (10 or 30mg/d) (Findling et al., 2008) to treat 13–17-year-old patients with schizophrenia. Clozapine (mean dose 176mg/d, SD 149 mg/d) is superior to both haloperidol (mean dose 16mg/d, SD 8 mg/d) (Kumra et al., 1996) and olanzepine (15–20mg/d) (Shaw et al., 2006)), particularly for negative symptoms in early-onset treatment resistant schizophrenia.

Although clinicians now infrequently prescribe typical neuroleptics to treat youth with schizophrenia, the first double-blind multisite randomly assigned trial that compared typical (molindone 10–40 mg/d) to atypical

neuroleptic drugs (risperidone 0.5–6mg/d, olanzepine 2.5–20mg/d) in 116 patients demonstrated no significant differences in response rates and symptom reduction between these medications (Sikich et al., 2008). This multisite study found a minimal effect of these drugs on cognitive function (Frazier et al., 2012). However, response to treatment within 3 weeks was a sensitive measure of clinical outcome in a 6-week randomized double blind trial of 186 youth with schizophrenia, aged 13–17 years treated with aripiprazole versus 96 patients of similar age given placebo (Correll et al., 2013). Nearly 50% of the change in psychotic symptoms occurred within two weeks and 75% of the change was evident within three weeks. The early responders had a significantly better outcome in terms of positive and negative psychotic symptoms, as well as in overall functioning than the nonresponders.

Regarding side effects, molindone alone was associated with akathisia (unpleasant feeing of restlessness and need to be in constant motion). But olanzepine showed the greatest risk for weight gain, as well as significant increases in fasting cholesterol, low-density lipoprotein, insulin, and liver transaminase levels. Double-blind evaluation of the long-term safety and efficacy of these three neuroleptics 44 weeks after the initial 8-week trial confirmed no significant efficacy differences or further symptom reduction following the 8-week initial trial. In contrast to the 8-week trial, in the follow-up study all three drugs were associated with weight gain, risperidone with increased prolactin, and molindone with akathisia. Of note, only 14 subjects (12%) of the original sample completed the study.

Despite the efficacy data, current available safety data highlight the short-term and long-term adverse effects of neuroleptics. The metabolic syndrome occurs with both typical and atypical neuroleptics, and increases the risk for diabetes mellitus and premature coronary artery disease (De Hert et al., 2009). Three of the five following criteria are needed to diagnose this syndrome: Obesity with BMI > 95th percentile, triglycerides > 110 mg/dL, high-density cholesterol < 40 mg/dL, fasting glucose > 100 mg/dL, and blood pressure > 90th percentile (see review in Correll, 2008).

A study of 338 neuroleptic naïve children and adolescents, aged 4–19-years, found significant weight gain (BMI > 95th percentile) in 10%–36% of the subjects with neuroleptic exposure of 7 days or less if treated with olanzepine, risperidone, quetiapine, or aripiprazole for a median of 10.8 weeks (Correll et al., 2009). Although the metabolic risk profiles varied across these drugs, there were more lipid than glucose abnormalities, rare diabetes and metabolic syndrome, and more severe weight gain and lipid abnormalities in olanzepine treated patients. The weight gain of clozapine treated schizophrenia youth falls between that of olanzepine and risperidone (see review in Correll, 2008). In addition to type of neuroleptic, polytherapy increases the likelihood of obesity, dyslipidemia, and type 2 diabetes based in 4140 children and adolescents prescribed 1 of 5 atypical or 2 conventional antipsychotics compared with a random sample of 4500 untreated children (McIntyre & Jerrell, 2008).

Despite the lack of long-term data on weight gain, the metabolic syndrome, and cardiovascular variables in neuroleptic treated youth, the reviewed safety findings justify the need to monitor weight, as well as lipid and glucose abnormalities in these patients. Correll & Kratchovil (Correll, 2008) suggest health screening and monitoring of patients treated with neuroleptics before starting treatment with subsequent repeat testing at 6 weeks, 12 weeks, and annually. They also recommend lifestyle changes in terms of diet and exercise for youth treated with neuroleptics.

Hyperprolactinemia, caused by both typical (haloperidol, pimozide) and atypical neuroleptics (risperidone > olanzepine > ziprasidone), impairs functioning of gonadotropins, estrogen, and testosterone by blocking D2 receptors in the tuberoinfundibular dopamine system of the anterior pituitary (see review in Roke, van Harten, Boot, & Buitelaar, 2009). Hyperprolactinemia occurs within 4–8 weeks of treatment onset and might persist for 1–2 years in patients treated with risperidone (Roke et al., 2009). Youth with a wide range of diagnoses, who are treated with neuroleptics, present mainly with gynecomastia and irregular menses. However, prolactinemia can cause gynecomastia, galactorrhea, sexual dysfunction, reduced fertility, decreased bone density, and osteoporosis. Treatment recommendations in symptomatic youth include neuroleptic dose reduction or crossover to aripiprazole, and use of bromocriptine or amantidine if symptoms continue (Correll, 2008).

Although considered infrequent, extrapyramidal symptoms including tremor, dystonia, akathisia, rigidity, withdrawal dyskinesia, and tardive dyskinesia also occur in youth treated with second-generation antipsychotics (see review in Correll & Kane, 2007). Treatment of these side effects includes anticholinergics (tremor, rigidity, and dystonia), beta blockers or benzodiazepines medications (akathisia), slow cross-titration (withdrawal dyskinesia), as well as dose change or switch to clozapine or preventive use of Vitamin E (tardive dyskinesia) (see review in Correll, 2008).

Neuroleptic malignant syndrome (NMS) is a serious, albeit rare, adverse effect associated with both typical (see review in Silva, Munoz, Alpert, Perlmutter, & Diaz, 1999) and atypical neuroleptics (see review in Neuhut, Lindenmayer, & Silva, 2009). The DSM-IV criteria include rigidity and hyperthermia with at least two of the following symptoms: diaphoresis, dysphagia, tremor, incontinence, tachycardia, tachypnea, hypertension, altering mental states from confusion to coma, and mutism. Laboratory findings include increased serum creatinine phosphokinase (CPK) and leucocytosis.

A case study review of 70 youth treated with typical neuroleptics (Silva et al., 1999) reported death in 9% and serious sequelae in 20% of the cases. However, there were no cases of death in a similar review of 20 youth treated with risperidone, olanzepine, and aripiprazole who had elevated CPK (Neuhut et al., 2009). Only 39% of these children met full NMS diagnostic criteria, while 47.8% presented with fever and rigidity. NMS onset was related to a recent increase in neuroleptic dose, and presented later and lasted less time in children treated with atypical compared with typical neuroleptics. Treatment involves neuroleptic withdrawal, fever reduction, intravenous hydration, and administration of bromocriptine. Use of anticholinergics and ECT in pediatric NMS needs to be further explored.

Finally, the recommendation for treatment of youth with schizophrenia is based on Class I data (see practice parameters in McClellan & Stock, 2013). Nevertheless, 75% of 1745 youth with schizophrenia and related disorders discontinue their medication when treated with aripiprazole, risperidone, quetiapine, olanzapine, or ziprasidone within 18 months (Findling et al., 2010). This is particularly important given evidence that symptoms recur in 77% of first episode patients within a year of stopping medication and in 90% within two years compared with 3% of patients who continue taking their drugs (Zipursky, Menezes, & Streiner, 2013).

Psychotherapy and Psychoeducation

Although few studies have been conducted on these treatment modalities in early-onset schizophrenia, psychotherapy focused on problem solving and coping with psychotic symptoms, psychoeducation for youth and their families and reintegration into school, and treatment of substance abuse facilitate rehabilitation and treatment adherence (see review in McClellan & Stock, 2013). The treatment approach should be tailored to the level of functioning and deficits experienced by the individual patient and how this affects family functioning.

Summary and Conclusions

- Psychopharmacological treatment is the only treatment modality studied to date for early-onset schizophrenia.
- 1st and 2nd generation antipsychotic drugs effectively treat positive symptoms but are less effective for negative symptoms and impaired cognition.
- Noncompliance is frequent, and most youth stop taking their medication within 18 months, mainly due to drug side effects.
- These include the metabolic syndrome (driven by weight gain), extrapyramidal symptoms, hyperprolactinemia, and the neuroleptic malignant syndrome.
- Supportive psychotherapy, psychoeducation, reintegration to school, cognitive rehabilitation, social skills training, and treatment for comorbid substance abuse where indicated are additional treatment modalities.

FUTURE DIRECTIONS

Since the late 1980s tremendous advances have been made in what we know about early-onset schizophrenia, albeit this has focused mainly on the biology of the disorder. Application of the developmental psychopathology principles (Cicchetti, 2006; Cicchetti & Toth, 2009) to future research on early-onset schizophrenia could pave the way for discovering biological and clinical illness markers needed for early identification of at-risk children. It would enable the development of biopsychosocial treatment modalities that impact the multiple levels of functional impairment found in these children. Incorporation of cultural context to these studies is essential for successful delivery of clinical services and for delineation of the different mechanisms involved in triggering onset of the disorder, its variable manifestations, and response to biological and psychological treatment modalities.

Principle 1: Interrelation Between Adaptive and Maladaptive Development with Special Attention to Resilience Despite Adversities, Genetic Loading, Psychosocial Problems

Despite the progress made on genetic abnormalities in early-onset schizophrenia, we still do not understand the role of psychosocial and demographic environmental variables and their interaction with genetic factors in

determining vulnerability or resilience to development of the disorder, trigger factors for onset and exacerbation of the disease, as well as its course and long-term outcome. In addition to delineating mechanisms underlying early-onset schizophrenia, the findings of prospective developmental studies on the interaction among adversities, genetic loading, and psychosocial problems in children at familial risk for schizophrenia could provide the background needed to develop focused psychosocial treatment studies.

In terms of risk factors and the need for early detection, the information available from birth cohort, offspring, and putative antecedents of schizophrenia studies reviewed in this chapter pertains primarily to adult onset of the disorder. Nevertheless, these studies clearly demonstrate that children with delayed developmental milestones in infancy and the toddler period as well as those with low IQ, impaired language, poor academic performance, and social difficulties during childhood might be at risk for schizophrenia. These variables are also risk factors for a wide range of psychopathology in children and adolescents. Therefore, large-scale prospective studies of children with these nonspecific risk factors could identify the different developmental and clinical profiles associated with the more common childhood and adolescent psychiatric disorders as well as the more rare early-onset schizophrenia.

Principle 2: Multiple Levels of Analysis Approach and an Interdisciplinary Perspective

The impact of early-onset schizophrenia on cognition, language, thinking, social skills, and motivation, the poor efficacy of antipsychotic drugs on these impairments, the adverse effects of these medications, and the high rate of noncompliance underscore the need for targeted rehabilitation studies. Cognitive rehabilitation, speech and language therapy, social skills training, and a positive behavioral approach can help improve the quality of life for children and adolescents with schizophrenia and their families.

As alluded to in the imaging section, cross sectional and longitudinal multidisciplinary, multimodal imaging studies on the broad range of functional impairments involved in youth with schizophrenia compared with their siblings and normal controls would provide important information on the disorder's abnormalities and the compensatory processes in the brains of nonaffected siblings with and without schizophrenia-related genetic findings. The findings of these studies could then be applied to design rehabilitation translational intervention studies (see Principles 3 and 5) focused on the stimulation of compensatory plasticity during ongoing brain development.

Principle 3: Theory and Empirical Research on Basic Biological and Psychological Developmental Processes Informs Prevention and Intervention Initiatives

Epidemiological and outcome studies are also warranted on youth with a wide range of illness severity to determine if, in fact, early-onset schizophrenia is a more severe disorder than the adult onset disorder. If confirmed, these findings would underscore the need for early identification and intervention.

Studies that demonstrate the structural and functional abnormalities of neural networks during ongoing brain development and their relationship with the symptoms and functional impairment of youth with early-onset schizophrenia will identify potential biomarkers of the disorder. These can then be used to identify at risk children and adolescents, to inform epidemiological and genetic studies, and to initiate preventive treatment.

Principle 4: Importance of Cultural Context for Study Designs and Quality Clinical Services

Although schizophrenia is a universal illness, studies are needed to determine the role played by cultural context in the illness's risk factors, triggers, clinical manifestations, dosing, efficacy, and safety of antipsychotic drugs, appropriate psychological treatment approaches, as well as in the imaging and genetic abnormalities. In addition to the theoretical importance of these studies, the relevance of cultural competence to timely detection, quality of care, and destigmatization of the disorder for these children and their families cannot be overstated.

Principle 5: Translational Research

The translation of basic science research findings have increased our knowledge about the pathogenesis of the disorder and its genetic basis, and led to the development of drugs that alleviate the illnesses symptoms. To date, little work has been done on the role of the social environment on brain development and on both behavior and early development in animal models of schizophrenia. Despite the translational limitations involved in animal model studies, they can provide important information on the

interaction of both early and late social environmental factors on the neurochemistry, histopathology, genetic, and imaging components of the disorder and its triggers in young animals.

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CHAPTER 22

Multilevel Approaches to Schizophrenia and Other Psychotic Disorders: The Biobehavioral Interface

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Sometimes I hear things that aren't there. Like when I'm laying in bed in the dark, I get scared to open my eyes because I hear a sound and I don't know what it is. Then I get the courage to open my eyes and find out it is just the fan.

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The opening quote comes from an adolescent boy who, within 2 years of this statement, was diagnosed with schizophrenia. He was experiencing the disturbing perceptions that were the prelude to the clinical onset of this often debilitating disorder. Schizophrenia and other psychotic disorders are among the most devastating of all mental disorders because the clinical symptoms typically arise when the patient is crossing the threshold into adulthood. These illnesses can derail the patient's developmental trajectory and thwart efforts to establish autonomy. In addition, the symptoms can interfere with functioning in critical domains: cognition, emotion, and social relationships.

Scientific advances in the field have led investigators to a clearer, albeit more complex, picture of the etiology of schizophrenia and other psychotic disorders than most would have imagined in the mid-twentieth century. First and foremost, the notion that psychotic disorders can be conceptualized as syndromes with a discrete onset, at either the behavioral or biological level, has given way to neurodevelopmental models of etiology (Cicchetti & Toth, 2009; Walker et al., 2013). While there is variability among contemporary models with respect to the behavioral and biological factors they emphasize, most share in common the assumption that congenital vulnerabilities, normal developmental processes, and environmental factors interact in the etiological process. Thus the onset of clinically defined psychosis is, in most cases, preceded by deviations from normal development in one or more functional domains. But these deviations are not uniform across cases, and the developmental trajectories vary with respect to the nature and severity of the abnormalities. Thus, the notion of equifinality, or multiple pathways to

the same clinical outcome, exemplifies psychotic disorders, as well as most other forms of psychopathology (Cicchetti, 2013; Cicchetti & Toth, 2009).

On the other hand, it has become apparent that the traditional diagnostic boundaries that have been drawn among subtypes of psychotic disorders do not map onto distinct etiologic pathways (Rasic, Hajek, Alda, & Uher, 2013). In fact, exemplifying the concept of multifinality, it has been shown that many risk factors, including genetic and psychosocial factors, are nonspecific and can give rise to multiple forms of psychopathology (Cicchetti & Toth, 2009). Due to the cumulative evidence that the various categories of psychotic disorders have overlapping etiologic pathways, the present chapter refers generally to psychosis or psychosis-spectrum disorders, rather than specifically to schizophrenia.

We begin our discussion with an overview of the symptoms and modal course of psychotic disorders and their associated cognitive deficits. We then turn to a discussion of the origins of vulnerability, an area where there have been the most dramatic changes in our scientific assumptions. This is followed by overviews of epidemiologic factors and postnatal environmental factors, the premorbid and prodromal stages, inflammation and stress, the premorbid and prodromal periods, neurobiological aspects of these illnesses, and treatment/intervention. We then turn to contemporary models of etiology, with an emphasis on the complex interplay among vulnerability, neurodevelopmental processes, and environmental triggers. Finally we examine directions for future research.

THE SYMPTOMS AND MODAL COURSE

By definition, psychosis entails a loss of contact with reality (American Psychiatric Association, 2013). The symptoms that reflect this are hallucinations, delusions, and thought disorder, as manifested in disorganized speech and disorganized behavior. These symptoms are often referred to as *positive symptoms* because they involve perceptions and ideations that are beyond those experienced by most people. Hallucinations are sensory experiences that are not associated with an external stimulus. They can occur in any sensory domain, but are most often auditory or visual. Delusions are false beliefs that are held with conviction despite conflicting evidence. They can range from generalized and relatively mundane notions (e.g., songs played on the radio are intended to have special messages for me) to specific and highly bizarre ideas about the world. Bizarre delusions are clearly implausible and do not derive from ordinary life experiences (e.g., aliens hired by the CIA have implanted transistors in the left hemisphere of my brain). Manifestations of disorganized speech include derailment, characterized by sequences of remotely related or unrelated ideas, and incoherence, such that the organization of the communication is so impaired that it does not convey meaning. Finally, disorganized behavior can be manifested in childlike silliness, unpredictable agitation, or abnormal motor behavior such as stereotypical movements or purposeless and excessive motor activity.

Negative symptoms are another general category of symptoms often associated with psychotic disorders. They reflect the absence or subtraction of elements of the normative experience of reality. Negative symptoms include blunted emotional expression or anhedonia, social withdrawal, alogia (decrease in speech), and avolition (decreased motivation). While negative symptoms are not required for a diagnosis of schizophrenia or any other psychotic disorder, they are present to varying degrees in most patients and contribute to the decline in functioning associated with psychoses.

Unlike previous versions of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), the fifth and most recent revision, the *DSM-5* (American Psychiatric Association, 2013) does not differentiate among subtypes of schizophrenia, but it continues to make distinctions among categories of psychotic disorders based on symptoms. The *DSM-5* lists five disorders in the category of Schizophrenia and other Psychotic Disorders: schizophrenia, schizophreniform, schizoaffective, delusional, brief psychotic disorder, psychosis due to another medical condition, and medication-induced psychotic disorder. The symptom criteria for these disorders are listed in Table 22.1.

As described in Table 22.1, the chief distinction among the categories of schizophrenia, schizophreniform, and brief psychotic disorder concerns the duration of the symptoms; the latter two disorders entail briefer durations. Delusional disorder is the most narrowly defined of the psychotic disorders, as it only requires one psychotic symptom (i.e., delusional belief). The *DSM-5* also makes a distinction based on presumed origins of the psychosis, and includes categories for psychotic symptoms due to a medical condition, such as dementia, and those induced by drugs. Given that the diagnostic criteria of most *DSM-5* psychotic disorders requires only one or two symptoms out of a list of several, two individuals may be diagnosed with the same disorder and not share a single symptom with one another. Thus, patients can vary dramatically in the A criteria for psychotic disorders, with one showing hallucinations

TABLE 22.1 Diagnostic Criteria for Schizophrenia and Other Psychotic Disorders (DSM-V, 2013)

Diagnostic Criteria for Schizophrenia

(A) Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be #1, 2, or 3 below:

1. Delusions.

2. Hallucinations.

3. Disorganized speech (e.g., frequent derailment or incoherence).

4. Grossly disorganized or catatonic behavior.

5. Negative symptoms (i.e., diminished emotional expression or avolition).

(B) For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

(C) Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

(D) Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

(E) The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

(F) If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Specify if:

The following course specifiers are only to be used after a 1-year duration of the disorder and if they are not in contradiction to the diagnostic course criteria.

- First episode, currently in acute episode
- First episode, currently in partial remission
- First episode, currently in full remission
- Multiple episodes, currently in acute episode
- Multiple episodes, currently in partial remission
- Multiple episodes, currently in full remission
- Continuous
- Unspecified

Specify if:

- With catatonia
  - Coding note: Use additional code 293.89 (F06.1) catatonia associated with schizophrenia to indicate the presence of the comorbid catatonia.

(*continued*)

TABLE 22.1 (Continued)

Diagnostic Criteria for Schizophreniform Disorder

(A) Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.

2. Hallucinations.

3. Disorganized speech (e.g., frequent derailment or incoherence).

4. Grossly disorganized or catatonic behavior.

5. Negative symptoms (i.e., diminished emotional expression or avolition).

(B) An episode of the disorder lasts at least 1 month but less than 6 months. When the diagnosis must be made without waiting for recovery, it should be qualified as provisional.

(C) Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

(D) The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Diagnostic Criteria for Delusional Disorder

(A) The presence of one (or more) delusions with a duration of 1 month or longer.

(B) Criterion A for schizophrenia has never been met.
- **Note:** Hallucinations, if present, are not prominent and are related to the delusional theme (e.g., the sensation of being infested with insects associated with delusions of infestation).

(C) Apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behavior is not obviously bizarre or odd.

(D) If manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods.

The disturbance is not attributable to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder, such as body dysmorphic disorder or obsessive-compulsive disorder.

Specify whether:

- Erotomanic type
- Grandiose type
- Jealous type
- Persecutory type
- Somatic type
- Mixed type
- Unspecified type

Specify if:

- With bizarre content

Specify if:

The following course specifiers are only to be used after a 1-year duration of the disorder:

- First episode, currently in acute episode
- First episode, currently in partial remission:

(*continued*)

TABLE 22.1 (Continued)

- First episode, currently in full remission
- Multiple episodes, currently in acute episode
- Multiple episodes, currently in partial remission
- Multiple episodes, currently in full remission
- Continuous
- Unspecified

Diagnostic Criteria for Brief Psychotic Disorder

(A) Presence of one (or more) of the following symptoms. At least one of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.
   - **Note:** Do not include a symptom if it is a culturally sanctioned response.

Duration of an episode of the disturbance is at least 1 day but less than 1 month, with eventual full return to premorbid level of functioning.
The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify if:

- With marked stressor(s) (brief reactive psychosis)
- Without marked stressor(s)
- With postpartum onset

Specify if:

- With catatonia
  - Coding note: Use additional code 293.89 (F06.1) catatonia associated with brief psychotic disorder to indicate the presence of the comorbid catatonia.

Diagnostic Criteria for Schizoaffective Disorder

(A) An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with Criterion A of schizophrenia.
   - **Note:** The major depressive episode must include Criterion A1: Depressed mood.

(B) Delusions or hallucinations for 2 or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness.

(C) Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of the illness.

(D) The disturbance is not attributable to the effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify whether:

- 295.70 (F25.0) Bipolar type: This subtype applies if a manic episode is part of the presentation. Major depressive episodes may also occur.
- 295.70 (F25.1) Depressive type: This subtype applies if only major depressive episodes are part of the presentation.

(*continued*)

TABLE 22.1 (Continued)

Specify if:

- With catatonia (refer to the criteria for catatonia associated with another mental disorder for definition).

Specify if:
The following course specifiers are only to be used after a 1-year duration of the disorder and if they are not in contradiction to the diagnostic course criteria.

- First episode, currently in acute episode
- First episode, currently in partial remission
- First episode, currently in full remission
- Multiple episodes, currently in acute episode
- Multiple episodes, currently in partial remission
- Multiple episodes, currently in full remission
- Continuous
- Unspecified

Diagnostic Criteria for Psychotic Disorders due to Another Medical Condition

(A) Prominent hallucinations or delusions.

(B) There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.

(C) The disturbance is not better explained by another mental disorder.

(D) The disturbance does not occur exclusively during the course of a delirium.

(E) The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify whether:
Code based on predominant symptom:

- 293.81 (F06.2) With delusions
- 293.82 (F06.0) With hallucinations

Diagnostic Criteria for Substance/Medication-Induced Psychotic Disorder

(A) Presence of one or both of the following symptoms:
   1. Delusions.
   2. Hallucinations.

(B) There is evidence from the history, physical examination, or laboratory findings of both (1) and (2):
   1. The symptoms in Criterion A developed during or soon after substance intoxication or withdrawal or after exposure to a medication.
   2. The involved substance/medication is capable of producing the symptoms in Criterion A.

(C) The disturbance is not better explained by a psychotic disorder that is not substance/medication-induced. Such evidence of an independent psychotic disorder could include the following:
   - The symptoms preceded the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after the cessation of acute withdrawal or severe intoxication; or there is other evidence of an independent non-substance/medication-induced psychotic disorder (e.g., a history of recurrent non-substance/medication-related episodes).

The disturbance does not occur exclusively during the course of a delirium.
The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

but no delusions, and another with the converse. This variability of symptom presentations within diagnostic categories is not unique to the latest edition of the *DSM* and is present in other categories of mental disorder (e.g., personality disorders). This within-category variability has probably contributed to the difficulty researchers have had in identifying disorder-specific etiologies.

In addition to the disorders listed in Table 22.1, the major mood disorders (i.e., depression and bipolar disorder) can be accompanied by psychotic features. To date, however, there is no strong evidence that these various categories of psychotic illness represent separate disorders with respect to etiology or neurobiological mechanisms. In fact, rapidly accumulating evidence from research on genetic and other etiologic factors indicates that, across the diagnostic boundaries, psychotic and several other mental disorders involve some shared etiologic factors (Craddock, O'Donovan, & Owen, 2009). We will discuss some of this evidence in greater detail.

In prior editions of the *DSM*, there were diagnostic criteria for a catatonic subtype of schizophrenia. In addition to the positive symptom criteria for schizophrenia, this category involved distinct abnormalities in posture and movement, such as motoric immobility, excessive and apparently purposeless motor activity, maintenance of a rigid posture (i.e., waxy immobility), mutism and unusual voluntary movement (e.g., posturing, stereotyped movements, prominent mannerisms, or grimacing). With the elimination of subtypes in the *DSM-5*, there are now separate diagnostic criteria for catatonia, and these are listed in Table 22.2. Thus, individuals can now meet diagnostic criteria for catatonia in addition to, and independent of, any other *DSM-5* diagnosis. This change reflects the increasing evidence that movement abnormalities are associated with a variety of mental illness, especially autism and psychosis spectrum disorders.

All categories of psychotic disorder show certain similarities in developmental course. One of their key epidemiological features is their onset in late adolescence/early adulthood (Carlson et al., 2002; Loranger, 1984). The risk rate for psychosis onset is very low prior to adolescence, then increases steadily with each year of age into the mid-20s. This has alerted researchers to the importance of neuromaturational processes in triggering the expression of psychotic symptoms. Coupled with the burgeoning research on significant brain developmental changes during this same period, most contemporary theories of the etiology of psychosis emphasize the role of adolescent neurodevelopment.

TABLE 22.2 Catatonia Associated with Another Mental Disorder (*DSM-V*, 2013)

The clinical picture is dominated by three (or more) of the following symptoms:

1. Stupor (i.e., no psychomotor activity; not actively relating to environment).
2. Catalepsy (i.e., passive induction of a posture held against gravity).
3. Waxy flexibility (i.e., slight, even resistance to positioning by examiner).
4. Mutism (i.e., no, or very little, verbal response [exclude if known aphasia]).
5. Negativism (i.e., opposition or no response to instructions or external stimuli).
6. Posturing (i.e., spontaneous and active maintenance of a posture against gravity).
7. Mannerism (i.e., odd, circumstantial caricature of normal actions).
8. Stereotypy (i.e., repetitive, abnormally frequent, non-goal-directed movements).
9. Agitation, not influenced by external stimuli.
10. Grimacing.
11. Echolalia (i.e., mimicking another's speech).
12. Echopraxia (i.e., mimicking another's movements).

While a diagnosis of psychosis is rare before the typical age of pubertal onset at about age 13, there is substantial evidence that the vulnerability for psychosis is present before the clinical syndrome emerges. Retrospective studies of diagnosed patients have revealed childhood academic performance deficits (Coi et al., 1993; Watt, 1970), signs of motor dysfunction (Walker et al., 1994), and socioemotional abnormalities (Walker et al., 1993, 2004) relative to their same-aged peers and healthy siblings. Thus behavioral indicators of vulnerability, usually subtle, are apparent long before the manifestation of clinical symptoms of psychosis.

During adolescence, the behavioral signs become more pronounced, and this is often the period when the prodrome emerges (Neumann et al., 1995). As will be described in greater detail, the prodrome is the period of functional decline and gradual emergence of symptoms that precedes the diagnosis of psychosis (Cannon et al., 2008). Lasting from months to years, the prodrome typically entails a decline in social, academic, and/or occupational performance.

The modal course of schizophrenia and other psychotic disorders, with symptoms typically appearing as the individual enters young adulthood, has led investigators to intensify their focus on neurodevelopmental processes in the prodrome that might be playing a role in triggering illness expression. Yet the more subtle signs of dysfunction that are often observed in childhood suggest that earlier developmental periods are also characterized by deviation from normal developmental trajectories.

Cognitive Impairment and Psychosis

In addition to the defining symptoms of psychosis, cognitive performance deficits are among the most common and challenging aspects of psychotic syndromes. Some consider these deficits to be a core feature of psychotic disorders (Barch & Ceaser, 2012). Yet, it is important to note that most patients score within the average range on cognitive tasks, although mean performance for patients is below that of healthy individuals of the same demographic background.

There is a now vast research literature documenting impairments in almost all areas of cognitive performance in patients with schizophrenia and other psychotic disorders (Bora, Yücel, & Pantelis, 2010). These performance deficits are observable on simple perceptual motor tasks, IQ tests, and measures of attention, memory, abstract thinking, and response inhibition. Other areas of deficits that have been the focus of a great deal of research are working memory and executive processes, such as planning and organization (Barch & Ceaser, 2012). Although cognitive deficits are apparent across diagnostic subtypes of psychosis and throughout the course of the illness, they are more pronounced the earlier the onset of illness, with those suffering from childhood onset psychosis having the most debilitating deficits (Frangou, 2013).

As would be expected, these impairments are a significant impediment to occupational functioning and it is unfortunate that they are generally not improved by pharmacologic treatments. Moreover, retrospective and prospective studies indicate that many patients manifest these deficits in childhood, and recent research suggest that they may become more pronounced in the period before the clinical onset of illness (Fusar-Poli et al., 2012; Reichenberg et al. 2010).

Among the cognitive problems associated with psychotic disorders, attentional deficits are among the most well-documented and subjectively distressing to patients (Mirsky et al., 1986; Nuechterlein et al., 2004). Attention deficit-hyperactivity disorder (ADHD) and psychotic diagnoses are highly comorbid (Elman et al., 1998; Kim-Cohen et al., 2003; Rubino et al., 2009). There is also a developmental link, in that a large proportion of those who go on to develop schizophrenia-spectrum disorders were diagnosed with ADHD during childhood. Ross and colleagues (2006) found that 84% of their sample of patients with schizophrenia had a prior childhood diagnosis of ADHD, though this estimate may be inflated due to the early mean age at onset for the sample. Nonetheless, this is a strikingly higher prevalence rate of ADHD as compared with the general population (around 5–6%; Polanczyk et al., 2007). Recently, a prospective study assessing the relative risk of later schizophrenia for those with a childhood diagnosis of ADHD concluded that children with ADHD were at a significantly increased risk for developing schizophrenia (RR = 4.3; Dalsgaard et al., 2013). Further, Rubino and colleagues (2009) showed that ADHD in childhood was even more predictive of schizophrenia than unipolar depression.

Social cognition, the ability to process social information and comprehend and solve interpersonal problems, is also impaired in psychotic patients. Mean performance on tests of facial and nonverbal emotion recognition, social relationship perception, and social problem solving is significantly below that of normative samples (Green et al., 2012). Within the domain of social cognition, an ability that has recently received a great deal of attention is theory of mind (ToM). This refers to the ability to accurately infer the feelings and thoughts of others. In the course of human interactions, ToM serves as the basis for empathy and understanding of the intentions of others. Individuals suffering from psychosis manifest significant deficits in ToM, and this poses problems for establishing and maintaining social relationships (Bora, Yucel & Pantelis, 2009).

There is little debate about the presence of cognitive deficits in psychosis, but their origins and significance remain unclear. The current consensus is that they are one aspect of vulnerability, in that they have been shown to precede the manifestation of clinical symptoms (Bora, Yücel & Pantelis, 2010). This view is consistent with the extensive evidence that vulnerability is typically congenital and arises in fetal brain development. Further, the cognitive impairments linked with schizophrenia and other psychotic disorders tend to persist after pharmacologic and psychotherapeutic treatment, and are associated with poorer prognosis. It has been shown that there are positive correlations among cognitive ability, insight, and social competence in psychosis, and that all of these factors are inversely correlated with clinical symptom severity (Quee et al., 2011). But the relation between cognitive factors and symptoms varies among symptom dimensions. A recent extensive review of the research literature indicates that negative and disorganized symptom dimensions are inversely, but modestly, correlated with cognitive functioning (correlations from –.29 to –.12), but that positive and depressive symptom severity are not associated with cognitive performance in samples of psychotic patients (de Gracia Dominguez et al., 2009). The authors conclude

that this indicates that the neural substrates responsible for disorganized and negative symptoms differ from those of positive and affective symptoms. Thus, cognitive capacity may moderate symptom expression in vulnerable individuals, but it does not appear to be a causal factor in the positive symptoms of psychosis. Researchers are examining the effects of cognitive rehabilitation on patients with psychotic illness, and the results of these efforts will shed further light on the role of cognitive deficit in the manifestation of psychotic symptoms.

THE ORIGINS OF VULNERABILITY TO SCHIZOPHRENIA AND OTHER PSYCHOSES

Over the past few decades, there have been major advances in our scientific understanding of congenital vulnerabilities to a host of human illnesses. Particularly in the realm of genetics, there has been a revolution in our understanding of how both genes and their expression are subject to a host of dynamic processes. Similarly, the prenatal environment has been shown to have pervasive effects on subsequent risk for a range of illnesses. For example, risk for diabetes in children is associated with maternal diet as well as maternal exposure to stress during pregnancy (Tamashiro et al., 2009). These and other findings have led researchers to consider the myriad of ways that developmental programming can occur during the fetal period and set the stage for later risk for morbidity (Gordon et al., 2011; Marques et al., 2013). In the following, we explore the genetic and prenatal environmental factors that give rise to vulnerability to psychosis and the complex interplay among them. These complex processes entail cycles of cross-talk between the environment and biological mechanisms, clearly demonstrating how permeable the boundary is between biology and behavior.

Genetics

Assumptions about the genetics of schizophrenia and other mental disorders have undergone a dramatic change as molecular genetic technologies have advanced. As recently as the 1980s, some investigators in the field of schizophrenia where continuing to debate the existence of a single risk gene for the disorder (Holzman et al., 1988). But as molecular genetic findings have accumulated, it has become clear that (1) there is no single or major risk gene; (2) that the genetic abnormalities that subserve vulnerability to schizophrenia are varied and complex; and (3) that mental disorders that have been viewed as belonging to distinct diagnostic categories actually share many genetic and environmental risk factors.

It now appears that genetic risk factors for schizophrenia and other psychotic disorders, as well as many serious developmental disorders, can be either inherited or acquired. With respect to acquired vulnerabilities, genetic risk sometimes results from aberrant processes that occur very early in the human life span, during the prenatal period, or even *prior to conception*. The evidence supporting these new conceptualizations is largely based on recent advances in our understanding of the genetic mechanisms of disease. Some are now referring to our contemporary view as the postgenomic era because we have moved beyond a focus on static DNA to a greater appreciation of dynamic genetic processes (Charney, 2012).

Beginning in the 1950s, findings from behavioral genetic studies using family, adoption, and twin paradigms all pointed to a significant role for genetic factors in schizophrenia (Gottesman, 1991). Family studies showed that risk for schizophrenia was elevated in biological relatives of patients with the disorder. The elevation in risk varied as a function of genetic similarity to the patient, with first-degree (parents, siblings) relatives having a greater risk than second degree, followed by third degree. Consistent with this, offspring of biological parents with schizophrenia who were reared by healthy adopted parents showed an elevated risk for schizophrenia. Finally, twin studies revealed that monozygotic (MZ) twins were significantly more likely to be concordant for schizophrenia than dizygotic (DZ) twins, with estimated concordance rates across studies varying from about 15–80% for MZ twins versus 5–20% for same-sex DZ pairs. Taken together, these findings were interpreted as providing strong evidence that an inherited genetic predisposition could be the basis of vulnerability. At the same time, with concordance rates for MZ twins being far below 100%, it was obvious that inherited genetic vulnerabilities were not telling the whole story.

There were, in fact, some puzzling aspects in the general pattern of findings. First, the concordance rates reported in MZ twins were highly variable across studies. A meta-analysis of the twin data revealed that several aspects of the study methodology, including the source of the twin samples, contributed to this variance (Walker et al., 1991). Further, the concordance rate for DZ twins, who have been assumed to be as genetically similar as siblings, was substantially higher than the concordance rate for siblings. Finally, the heritability estimates yielded by twin, adoption, and family studies differed, with twin studies being higher than the other methods (Walker et al., 1991).

New findings on the preconception and prenatal factors that influence genes and gene expression are bringing the source of these discrepancies into clearer focus.

Once procedures for genotyping became more widely available in the 1980s, researchers had the opportunity to identify specific risk genes and variants (Owen et al., 2010). By way of background, single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) are often the focus of these studies. A SNP is a DNA sequence that can vary, such that a single nucleotide (i.e., A, T, C or G) in the genome differs among individuals or between chromosome pairs. Thus, there are at least two alternative forms (i.e., alleles) of the gene at the same locus. CNVs are a type of structural variation in the genome, a change in the sequence of nucleotides, in which the DNA in the cell has an abnormal number of copies of one or more sections of the DNA. CNVs can be inherited or can arise through de novo, or spontaneous, mutations.

When considering the role of mutations in illness, it should be emphasized that, although they are essentially errors in the DNA code, they are not always disadvantageous, and in fact are assumed to be the basis for adaptive evolution. Nonetheless, when the mutation results in changes in one or more proteins essential for cellular survival or normal brain function, the consequences are typically negative (Schon, DiMauro, & Hirano, 2012; Veltman & Brunner, 2012). The causes of mutations are not yet fully understood, but it is now assumed that some occur randomly (stochastic processes), whereas others are a function of exposure to mutagens, most notably radiation and chemical exposures. Further, they can originate in germ cells (eggs and sperm) or in somatic cells.

Initially genotyping studies appeared to hold great promise, and investigators reported that alleles of genes, such as DISC1 (disrupted in schizophrenia 1), COM-T (catechol-o-methyltransferase) and NRG-1 (neuregulin 1), were linked with variations in risk for schizophrenia, as well as affective psychosis (Craddock, O'Donovan & Owen, 2005). But the effect sizes for these genes were very small and, although statistically significant with sufficiently large samples, accounted for a very small proportion of the variance. Further, the same genes have been found to confer risk for a variety of psychiatric disorders, as well as biological sensitivity to stress (Walder et al., 2010). Investigators have continued this search over the past three decades, but the results have been disappointing in that individual genes or combinations of genes that had been fairly consistently shown to be linked with schizophrenia ultimately amounted for only a small proportion of risk (Gershon, Alliey-Rodriguez, & Liu, 2011). A recent genome-wide association study (GWAS) revealed 13 new loci associated with risk for schizophrenia, leading the authors to conclude that "8,300 independent, mostly common SNPs (95% credible interval of 6,300–10,200 SNPs) contribute to risk for schizophrenia and that these collectively account for at least 32% of the variance in liability" (Ripke et al., 2013, p. 1150). Taking a somewhat different perspective, researchers reporting another recent GWAS study of both SNPs and CNVs concluded that "rare deleterious variants may be more important in schizophrenia predisposition than common polymorphisms. While our analyses do not suggest that implicated CNVs impinge on particular key pathways, we do support the contribution of specific genomic regions in schizophrenia, presumably due to recurrent mutation. On balance, these data suggest that very few schizophrenia patients share identical genomic causation, potentially complicating efforts to personalize treatment regimens" (Need et al., 2009, p. 1).

At the same time these studies of the genetics of psychosis were under way, new discoveries were revolutionizing perspectives on genetic mechanisms in disease (Charney, 2012). First, it was discovered that genetic mutations, including CNVs, were much more common than had been assumed: some of these originated in germ cells (sperm and ova), and were thus inherited by offspring even though not present in the parent's somatic cells, and others arose spontaneously during embryogenesis, or perhaps later. Second, researchers began to make great strides in understanding the processes whereby gene expression is regulated, giving rise to the field of *epigenetics*. Like mutations, epigenetic changes can be inherited or acquired in the developmental course of the individual. It now appears that both mutations and epigenetics are relevant to our understanding of schizophrenia and other psychotic disorders, and they may explain the puzzling aspects of findings from earlier behavior genetic paradigms.

As noted already, CNVs are one type of mutation. These sometimes entail a deletion in which a part of a chromosome or DNA sequence is missing. Deletions can range from a single base to an entire piece of chromosome, and can be caused by errors in the crossover of chromosomes during meiosis. As early as 1953, Book suggested that mutations might be a source of the genetic abnormalities contributing to schizophrenia. But at the time it was assumed that mutations were not common enough to account for schizophrenia or other common mental illnesses because of the relatively high rate of occurrence of these disorders in the population. But with contemporary techniques for examining genotypes, researchers have discovered that mutations are more common than

had been previously assumed, and they are now able to identify individual and group differences in the proportion of mutations. Studies comparing healthy individuals to patients with schizophrenia and other psychoses have shown that the patients have significantly more CNVs including deletions (Bassett, Scherer, & Brzustowicz, 2010; Rees, Kirov, O'Donovan, & Owen, 2012). In other words, there are more coding errors in their genes. Further, these mutations have been observed on multiple chromosomes and in a range of mental disorders, from autism to adult-onset psychosis (Rapoport, Giedd, & Gogtay, 2012). Thus, to date, there is little evidence of specificity of mutations to schizophrenia or other psychotic disorders, although one trend in the genetic findings is that genes involved in brain development are among those most often linked with mental illness.

The findings of shared genetic abnormalities in autism spectrum and psychosis spectrum disorders are especially challenging to the diagnostic boundaries drawn by current diagnostic taxonomies, including the *DSM-5*. Recent research on genetic deletions has revealed numerous areas of overlap for the two disorder spectra (Adwalla et al., 2010; Burbach & van der Zwaag, 2008; King & Lord, 2010). Examples include the 15q13.3 deletion (Pagnamenta et al., 2009; Stefansson et al., 2008), 16p11.2 deletions and duplications (McCarthy et al., 2009; Weiss et al., 2008), deletions in Neurexin 1 (NRXN1; Ching et al., 2010; Kim et al., 2009; Kirov et al., 2008) and 22q11.2 deletions (Ousley et al., 2013).

The 22q11.2 deletion is one of the most studied in relation to psychosis and autism spectrum disorders (ASD), and it is currently the most predictive genetic risk factor for both. 22q11.2 deletion syndrome (DS) occurs in approximately 1 out of every 4,000 births, and presents variable physical phenotypes, including heart defects, cleft palate, immune deficiencies, skeletal abnormalities, and minor facial anomalies (Esterberg, Ousley, Cubells, & Walker, 2013; Philip & Bassett, 2011; Wilson et al., 1994). Individuals with 22q11.2 DS have been shown to be at a heightened-risk of developing psychosis and ASD, as well as experiencing subclinical symptoms of these disorders. For example, in a sample of adolescents with 22q11.2 DS, 45% experienced attenuated psychotic symptoms, 85% endorsed moderate negative symptoms, 55% experienced disorganized symptoms, and 25% had a diagnosis of ASD (Stoddard, Niendam, Hendren, Carter, & Simon, 2010). When examined for prodromal signs of psychosis, 60% of the 22q11.2 DS individuals met criteria for being at clinical high-risk of developing psychosis (Shapiro, Cubells, Ousley, & Walker, 2011). Given the high percentage of individuals with 22q11.2 DS endorsing psychotic or prodromal signs, it is of no surprise that several studies found that around 30% of individuals with 22q11DS develop psychosis (Antshel et al., 2010; Gothelf et al., 2007; Kates et al., 2011). In some cases, individuals with 22q11.2 DS have comorbid diagnoses of psychosis and ASD (Vorstman et al., 2006). Ousley and colleagues (2013) reported that 40% of their 22q11.2 DS sample that met criteria for ASD also met criteria for a schizophrenia-spectrum disorder, although using more stringent diagnostic criteria for ASD yielded a 20% comorbidity rate.

Clearly, the co-occurring psychotic and autistic symptomology in 22q11.2 DS highlights our need to further investigate the etiological commonalities between psychosis and ASD, as well as the factors that result in such different developmental trajectories. Karayigorgou and colleagues (2010) have suggested that some children with 22q11.2 DS manifest autistic behaviors as part of a prodromal syndrome that precedes the later onset of psychosis. It has also been suggested that the elevated rates of both psychotic disorders and ASD in 22q11.2 DS serve as an example of neuropsychiatric *pleiotropy* (Vorstman et al., 2013). While the term pleiotropy has typically been used to refer to divergent phenotypic manifestations resulting from a single genetic variant, in the case of 22q11.2 DS, there are varied phenotypic manifestations of a specific chromosomal deletion. These varied manifestations are presumably a reflection of gene–gene interactions and gene–environment interactions, as well as individual differences in gene expression profiles, as we will discuss further.

With respect to the origins of mutations, many originate in germ cells of the parents, while others arise in the individual's somatic cells. In the case of germ-line mutations, the parent may acquire a mutation in ova or sperm that is not present in their somatic cells, but is passed on to offspring. The mutation can then be present in the somatic cells of the child. In 2001, Malaspina and colleagues reported evidence that advanced paternal age was associated with heightened risk for schizophrenia in offspring (Malaspina et al., 2001) and this has been replicated by other research groups (Miller et al., 2011). In a recent review of the literature on paternal age, the authors conclude that: "This risk factor increases the risk of schizophrenia as much as any single candidate gene of risk" (Miller et al., 2011, p. 1039). Subsequent studies have found the same link for autism (Hultman et al., 2010; van Balkom et al., 2012) and for intellectual disabilities (Saha et al., 2009). More recently, research has directly verified the genetic mutations mediating these

relations; several studies of large samples have revealed that advanced paternal age is indeed associated with a higher rate of mutations in somatic cells of offspring (Kong et al., 2012). The relation has also been observed for maternal age by some research groups, although the effect is not as great, presumably due to the higher rate of cell divisions in spermatogenesis than in egg production (Kong et al., 2012). Taken together, the previous findings are important, because they demonstrate that genetic abnormalities subserving vulnerability can originate in the *prezygotic period*. In other words, vulnerability can be conferred prior to conception.

Although a plethora of environmental factors can give rise to germ-line mutations, the most well established classes of environmental factors are chemical and radiation exposure (Pacey, 2010; Yauk et al., 2012). Other germ-line mutations result from errors that occur randomly during cell division, especially in spermatogenesis (Kong et al, 2012). As mentioned, mutations can also occur in somatic or body cells (Schon, DiMauro, & Hirano, 2012). These mutations can arise during embryogenesis when cells are rapidly dividing, and may result from environmental factors, such as prenatal or postnatal exposure to drugs and radiation (Veltman & Brunner, 2012).

The adverse effects of mutations result from the protein production abnormalities they can trigger. Thus DNA, whether intact or mutated, affects functioning via gene expression and the production of proteins. But mutations are not the only source of aberrant protein production. There are multiple biological processes that determine gene expression, and DNA code is only one of these. Rapid progress in the understanding of these processes over the past decade has resulted from studies of epigenetics.

Epigenetics is concerned with the processes involved in the expression of genes, and its study has revolutionized perspectives on the causes of mental disorders (Cortessis et al., 2012). Broadly defined, epigenetics refers to the regulation of factors associated with gene expression that are not encoded within the DNA sequence (for reviews, see Gudsnuk & Champagne, 2011; Monk et al., 2012; Szyf, 2012). The two primary epigenetic processes through which genes are expressed or silenced are *DNA methylation* (addition of a methyl group to the cytosine or adenine DNA nucleotides) and remodeling of chromatin structure by chemically modifying *histones* (proteins in cell nuclei that package and order DNA into structural units; Gudsnuk & Champagne, 2011).

DNA methylation entails alterations of the DNA sequence at specific regions of the gene by enzymes known as DNA methyltransferases (DNMTs) (Jaenisch & Bird, 2003). Methylation of DNA generally *decreases* the accessibility of DNA for transcription, resulting in gene silencing. Histone modification involves chemical processes occurring at protein tails (i.e., residues of proteins) that project from histones, but the ways histones can be altered are highly complex—sufficiently complex as to be referred to as the histone code (Jenuwein & Allis, 2001). Changes at histone tails result in the modification of chromatin structure. For instance, histone acetylation opens up the chromatin, allowing the DNA transcription factors to bind and *activate* gene expression. Conversely, histone deacetylation works to condense the chromatin structure, making it much more difficult for transcription factors to access the DNA and thereby *decreasing* gene expression. It is important to note that DNA methylation and histone modification, while representing two distinct epigenetic mechanisms, are not wholly separable processes. Rather, it has been shown that DNA methylation can lead to chemical changes that result in histone deacetylation, and that certain unacetylated histones can attract DNA methyltransferases, both of which further contribute to gene silencing (Rutten & Mill, 2009).

Epigenetic mechanisms are most active early in embryonic development, playing an essential role in cellular differentiation (for review, see Szyf, 2012), but these processes remain dynamic over the course of the life span (Szyf, 2012; Gudsnuk & Champagne, 2011; Monk et al., 2012; Roth & Sweatt, 2011). Further, epigenetic modifications are heritable and reversible (Gudsnuk & Champagne, 2011; Roth et al., 2009; Monk et al., 2012; Pan, Lai, Wu, & Ho, 2013), thus elucidating epigenetic processes in disease is an important area of inquiry for both understanding the etiology of disorders and shedding light on options for preventive intervention.

Several recent reviews have summarized the evidence that adverse early experiences affect epigenetic processes both in animal models and in humans (Monk et al., 2012; Roth et al., 2011; Szyf, 2012). Carefully controlled laboratory studies with animals (primarily rodents), focusing on methylation patterns in a variety of genes implicated in psychiatric disorders, have provided valuable insight into the impact of early life experiences on possible pathogenic processes. For example, adverse early postnatal experiences affect expression of the gene for brain-derived neurotrophic factor (BDNF), a neurotrophic factor that appears to be reduced in schizophrenia, depression, and anxiety disorders (for recent reviews, see Gray et al., 2013; Roth et al., 2011). When compared with controls, infant rats exposed to nonoptimal rearing or maternal stress manifest both hypermethylated prefrontal BDNF DNA

and a reduction in prefrontal BDNF mRNA as adults. Further, Roth and colleagues (2011) demonstrated that the abnormal BDNF methylation and gene expression caused by early maltreatment was reversible when they administered zebularine, a DNA methyltransferase (DNMT) inhibitor. These findings illustrate the dynamic nature of epigenetic processes and how a targeted treatment has the power to undo the deleterious impact of adverse early life experience.

Although research on epigenetic processes in primates is limited, compared with rodent studies, there is increasing evidence of similar relations between environmental factors and gene expression in humans. For example, in a recent study of DNA methylation in the peripheral blood cells of a Canadian community cohort, demographic factors (e.g., sex, age, and ethnicity) and psychosocial factors, such as early life stress and current perceived stress, were significantly associated with methylation levels (Lam et al., 2012). Also of interest for understanding the pathogenic processes of psychiatric illnesses was the finding from this study that cortisol output was associated with variations in DNA methylation. Further research aimed at replicating these results is critical, because they may have significant implications for preventive intervention.

Unlike animal studies, which have analyzed epigenetic profiles directly in brain tissue, the Lam et al. (2012) study used blood samples to ascertain DNA methylation levels,. While brain tissue analysis is typically not feasible with human subjects, there are two postmortem studies that have assessed DNA methylation in human hippocampal tissue (McGowan et al., 2009; Labonté et al., 2012) taken from suicide completers with and without histories of child abuse, as well as non-suicidal controls. McGowan and colleagues (2009) examined both methylation and mRNA levels of the NR3C1 gene, which encodes the glucocorticoid receptor (GR), and found that suicide completers with a history of child abuse exhibited increased methylation at an NR3C1 promoter, as well as reduced expression of GR mRNA. Extending this work, Labonté et al. (2012) conducted a genome-wide analysis of epigenetic markers and mRNA levels in hippocampal tissue from the same sample and found 362 promoters that were differentially methylated (248 hypermethylated and 114 hypomethylated) in suicide completers with a history of abuse versus controls. Genes involved in neuronal plasticity were more strongly differentially methylated. These findings suggest that adverse early life experiences may have an enduring impact on gene expression in the human brain.

Research is recently yielding evidence about epigenetic changes associated with psychosis. Several groups have reported DNA methylation differences between psychotic patients and controls in postmortem studies of brain tissue (for reviews, see Labrie et al., 2012; Syrakic et al., 2013). Perhaps most compelling, comparisons of MZ twins who are discordant for schizophrenia reveal patterns of gene expression in blood cells that differentiate the co-twins. For example, a study comparing MZ twins discordant for schizophrenia or bipolar disorder with psychosis showed numerous loci with illness-associated DNA methylation differences between the co-twins within pairs, as well as between the groups of affected and non-affected twins (Dempster et al., 2011). The epigenetic changes were most pronounced in genes governing the functions of biological networks and pathways that have been hypothesized to be involved in psychiatric disorders and neurodevelopment. The general pattern was significantly hypomethylated regions in affected twins, most notably in the promoter of a gene (ST6GALNAC1—gene-encoding alpha-*N*-acetylgalacto saminide alpha-2,6-sialyltransferase 1) that has been implicated in psychosis. Although some methylation differences were found across all discordant twin pairs for both diagnostic categories, others were specific to one or a couple of pairs. Further, some regions were consistently altered when the combined discordant psychosis group was compared with unaffected co-twins, whereas others were specific to either schizophrenia or bipolar disorder.

Another study examined DNA methylation markers in blood from schizophrenia patients and healthy controls (Lui et al., 2013). After controlling for demographic factors and substance use, the researchers found diagnostic group differences in patterns of hyper- or hypomethylation, and these were validated using an independent data set. There were seven genes with expression levels that were significantly altered in patients (patients showed hypomethylation/upregulation in TCN1, and hypermethylation/downregulation in CD244 and CBFA2T3, and downregulation with hypomethylation in CD244 and CBFA2T3). Within the patient group, the methylation patterns were not associated with disorganized or negative symptoms, but they were correlated with delusions and hallucinations. The pattern of correlations suggested that methylation changes may play a protective role in lessening the severity of delusions and hallucinations in patients. Further analyses showed that the differentially methylated genes are involved in the inflammatory response (i.e., activations of T-cells, B-cells, and natural killer cells or in cytotoxic reaction). Later in this chapter, we discuss other evidence and theories linking immune system dysfunction with psychosis.

In sum, there is no doubt that the study of epigenetics holds tremendous promise for elucidating the determinants of normal and abnormal brain development, as well as the origins of human disease. Yet, methodological challenges must be considered; Epigenetic changes can be a consequence, rather than a cause, of the phenotype of interest. It has been shown, for example, that antipsychotic medications are associated with epigenetic changes (Melas et al., 2012), and all studies to date of epigenetic phenomena in psychosis have primarily included medicated patients. Other environmental exposures linked with epigenetic changes include drug use, stress, and nutritional deficiency, all of which have been shown to be associated with serious mental illness (Holtzman et al., 2013; Kirkbride et al., 2012; Rotter et al., 2012). To disentangle these factors, there is a need for prospective, longitudinal investigations that track epigenetic profiles in individuals at risk for psychosis who have not been exposed to medication and whose environmental exposures across development are documented. As will be described, studies of youth who manifest clinical high-risk syndromes are currently under way and may be the optimal paradigm for tracking epigenetics.

As noted already, the heritability estimates for psychosis based on twin, adoption, and family studies were substantial, yet puzzling in their discrepancies. Moreover, subsequent studies of candidate risk genes, as well as genome wide scans, were not successful in identifying genes that accounted for more than a very small proportion of the phenotypic variance. The findings on mutations and epigenetics, described previously, have shed light on the sources of these discrepancies. In an important paper, Evan Charney (2012) systematically reviewed the potential impact of mutations and epigenetic processes on phenotypic variance in MZ and DZ twins. In particular, he shows how the assumption of equal environments, the basis for the twin study method, does not take these processes into consideration. First, germ-line mutations and germ-line epigenetic profiles resulting from environmental factors are more likely to be shared by MZ than DZ twins. Second, the intrauterine environment is more similar for MZ twins than DZ twins because MZ pairs can share a placenta and chorion (about 2/3 of MZs), as well as an amniotic sac, whereas DZ twins do not. Thus, when shared, placental abnormalities can affect both members of MZ twin pairs. All of these environmental factors contribute to inflated heritability estimates in twin studies. In contrast, in the minority of MZ twin pairs in which the two members have separate placentas, there is greater gene expression discordance at birth (Gordon et al., 2011). Genes previously defined as being involved in response to the external environment showed the most variable expression within pairs, independent of cell type, supporting the idea that even slight differences in intrauterine environment can influence expression profiles.

Further, Charney (2012) reviewed the extensive evidence that the fetal and infant morbidity and mortality rates are highest for MZ twins, intermediate for DZ twins, and lowest for singleton births. The elevated morbidity and mortality rates in twins, especially MZ pairs, are attributed to higher levels of obstetric complications and maternal stress. Phenotypic concordance for developmental disorders and brain morphology shows the same pattern; MZ > DZ > sibling pairs. Thus, twins in general are exposed to a less optimal environment than singletons, and MZ twins have the highest rate of complications, especially when they are monochorionic. The result is greater stress-induced phenotypic concordance in MZ than DZ twins, and in DZ twins compared with singletons. In the next section, we review the evidence that the prenatal environment, including maternal stress exposure, is associated with risk for psychosis.

In summary, the results of research on the genetics of schizophrenia and other psychotic disorders have not revealed any heritable risk alleles of large effect, and those that have been identified confer vulnerability for other disorders, as well as generalized stress sensitivity (Walder et al., 2010). Advances in our understanding of mutations and epigenetics have helped to shed light on other sources of genetic risk, as well as environmental factors that might determine them.

The Prenatal Environment

Against the backdrop of our contemporary understanding of genetics, it is not surprising that there is extensive evidence of greater obstetric complications and adverse prenatal events in individuals who subsequently develop psychosis. The human genome is especially susceptible to mutations during embryonic and fetal development, and epigenetic processes are pivotal in determining the development of the nervous system.

Research has documented a relation between multiple obstetric complications and prenatal events and the subsequent risk of schizophrenia and affective psychosis in offspring (Buka & Fan, 1999; Cannon et al., 2002). Among the prenatal complications that are associated with elevated risk are bleeding, diabetes, rhesus incompatibility, preeclampsia, and maternal viral infection (Brown & Derkits, 2010). Similarly, studies of nutritional deficiency during pregnancy, such as exposure to the Dutch famine, have revealed a higher rate of psychosis in the offspring

(Kirkbride et al., 2012). Delivery complications, especially prolonged labor, are also more common (Buka & Fan, 1999). Finally, the maternal experience of stressful events during pregnancy, such as traumatic personal or natural disasters, heightens the risk for psychosis in offspring (Markham & Koenig, 2011; Van Os et al., 2010).

All of the previous prenatal factors are assumed to heighten risk via their effects on fetal brain development. Although the precise mechanisms are not known, hypoxia is assumed to mediate some of the effects of prenatal and delivery complications (Fineberg et al., 2012), and inflammatory processes have been hypothesized to be involved in the effects of prenatal maternal infection (Miller et al., 2013). Nutritional deficiency is known to compromise fetal brain development, and recent results from animal studies suggest how epigenetic processes might mediate this effect (Kirkbride et al., 2012). With regard to maternal stress, it is assumed that increased maternal cortisol secretion plays a role, partially through inflammatory pathways and also via epigenetic processes that affect the development of brain structure and stress systems in the fetus (Markham & Koenig, 2011; Van Os et al., 2010). In a section to follow, we consider in greater detail the role of brain stress systems in psychosis.

One of the questions raised with regard to the effects of obstetric complications and prenatal events on risk for psychosis is whether they are sufficient to confer vulnerability. Specifically, do they interact with a preexisting genetic liability, or can they give rise to vulnerability independent of genetic risk? There is some evidence of a gene–environment interaction, such that individuals with a family history of schizophrenia may be more susceptible to the adverse effects of prenatal insults (Clarke et al., 2009). Yet there are also findings suggesting the prenatal complications are more common in patients without a family history of psychiatric illness (Cantor-Graae et al., 1994). In fact, in light of our current understanding of epigenetics, the question of whether prenatal complications can confer vulnerability independent of genetic factors should be reconceptualized. It is indeed possible that prezygotic and prenatal factors can cause mutations and epigenetic changes that constitute genetic risk for psychosis. While there are currently no research findings that directly address this issue, it is likely that there will be in the near future.

In summary, initial assumptions about the origins of vulnerability to psychotic disorders were highly simplistic, by contemporary standards, and were limited by the narrow scope of our understanding of genetics and neurodevelopment. The initial focus on single causal genes or small subsets of risk genes has given way to evidence that the processes that give rise to vulnerability are far more complex than assumed and probably entail intricate interactions between environmental and biological factors. In light of the evidence, it appears likely that there are multiple pathways to vulnerability. Thus the etiological processes that confer risk will vary among psychotic patients. Further, environmental risk factors show regional variation, so it is not surprising that there are some national and ethnic differences in risk for schizophrenia.

EPIDEMIOLOGY AND POSTNATAL ENVIRONMENTAL EXPOSURES

Epidemiology

Although there are some national variations, the prevalence and modal age at onset of psychosis, especially schizophrenia, is strikingly consistent across cultures, with lifetime rates of 1.4–4.6 per 1000 across cultures (Jablensky, 2000). This has prompted some theorists to view psychosis as a uniquely human disorder that involves common species-specific genetic factors and brain developmental processes (Crow, 2012).

Nonetheless, there are regional and demographic differences in the risk. For example, across countries, urban and migrant populations have somewhat higher rates of psychosis and other serious mental disorders (McGrath et al., 2004; van Os, Kenis, & Rutten, 2010). Further, within nations, immigrant status, particularly for ethnic minorities, is linked with a significantly higher risk-rate for psychosis (Dealberto, 2010). While the reasons for this are not clear, there is some evidence that perceived discrimination may be a mediating factor (Morgan et al., 2010). Trauma and stress are significantly associated with psychosis risk, and perceived discrimination may be one source of psychosocial stress.

Drug exposures may also contribute to population differences in psychosis risk. Reviews of the research literature on cannabis and psychosis conclude that cannabis use is associated with an increased risk for psychosis (Moore et al., 2007). It also appears to be linked with an earlier age at onset of psychosis (Compton et al., 2009; Large et al., 2011). The tetrahydrocannabinol (THC) content in cannabis, its major psychoactive agent, has similarly been linked with psychosis risk and psychotomimetic effects (van Os, Kenis & Rutten, 2010). Cross-national comparisons have shown that variations in age at onset and risk for psychosis are associated with differences in cannabis use, and higher THC levels are associated with greater risk (Hall & Degenhardt, 2009).

Of course, the correlational nature of these data precludes strong causal inferences. Individuals at risk for psychosis may be drawn to the use of recreational drugs for self-medication or because they are more often in social contexts where drugs are accessible. Alternatively, drug use may actually be increasing the likelihood of psychosis. Two recent reviews of the longitudinal cohort studies (LeBec et al., 2009; McLaren et al., 2010) and one new cohort study with repeated assessments (Kuepper et al., 2011) all concluded that cannabis use can increase risk for psychosis onset and persistence. At the level of neurobiology, findings from experimental research with animals and a few studies of humans suggest that cannabis-induced changes in brain DA activity may be involved in the link with psychosis, but this is considered tentative (Kuepper et al., 2010).

Like cannabis, stimulant use is related with risk for psychosis. This was originally noted in research conducted following widespread increases in methamphetamine use in Japan (Sato, Numachi, & Hamamura, 1992). A recent population-based study showed that all drug use was associated with a higher risk rate for schizophrenia, but that methamphetamine use and cannabis use were linked with higher rates than cocaine, opioid, and alcohol use (Callaghan et al., 2012). The well-established relation of methamphetamine use with psychosis has raised concerns about the increasing rates of prescription stimulant use among youth, particularly given that those who are at risk for psychosis are more likely to be diagnosed with ADHD. Although there is not yet sufficient research to estimate the effect of prescription stimulants on psychosis rates, there are case reports that suggest the presence of prescription stimulant-induced psychosis (Lakhan & Kirchgessner, 2012). This is likely to be a focus of increasing research as large cohorts of youth on prescription stimulants enter the risk period for the onset of psychosis. As is the case for cannabis, the down-stream effects of stimulants, particularly on dopamine (DA) activity, suggest a likely mediating process.

Sex differences in psychosis, particularly schizophrenia, are well-established. Males tend to have an earlier age at onset of psychosis, and the prognosis for males is poorer than for females (Abel, Drake & Goldstein, 2010). In part, this is likely due to the higher rate of substance use, the lower rate of treatment compliance, and the lower levels of social support that characterize male versus female patients (Masand et al., 2009). In addition, it has been suggested that estrogen may have a protective effect for females in that it acts to reduce DA activity (Abel, Drake, & Goldstein, 2010).

Another domain of factors that has been shown to increase vulnerability for psychosis is exposure to brain damage. Both traumatic brain injury (TBI; Molloy, Conroy, Cotter, & Cannon, 2011) and childhood viral infections of the central nervous system elevate the risk of psychosis (Khandaker, Zimbron, Dalman, Lewis, & Jones, 2012). The meta-analysis by Molloy and colleagues (2011) showed an increased risk of schizophrenia following TBI, as well as a more pronounced effect in those with a genetic predisposition to psychosis. The latter suggests a gene–environment interaction.

It has long been established that, in general, patients diagnosed with psychotic disorders have significantly lower rates of marriage and reproduction than the general population, and this is especially pronounced for males (Bundy, Stahl & MacCabe, 2011; Power et al., 2013). The earlier onset and poorer prognosis for psychosis in males may explain the sex difference in both marriage and reproduction. Whatever the origin of this sex difference, it is clear from the data that neither male nor female patients with psychosis and other serious mental disorders reproduce at replacement levels (Power et al., 2013), yet epidemiological studies show stable incidence rates for psychotic disorders across cohorts (Kirkbride et al., 2012) . These findings are inconsistent with the assumption that risk for psychosis is highly heritable and has raised questions about how risk genes for schizophrenia are maintained across generations. The data on reduced fertility are, however, consistent with contemporary findings on the mutations and epigenetic processes that confer vulnerability for psychosis.

The Postnatal Psychosocial Environment: Trauma and Stress

The diathesis–stress model has been a long-standing frame of reference for conceptualizing the etiology of schizophrenia (Walker & Diforio, 1997). It assumes that vulnerability, the diathesis, originates in genetic and prenatal factors, such as those previously discussed. Then, as development ensues, the clinical expression of the diathesis is triggered by environmental factors. We have already seen that maternal stress exposure during pregnancy is related to greater risk for psychosis in offspring. In addition, postnatal trauma and psychosocial stress appear to be important triggering factors.

There is now a large body of retrospective reports demonstrating that childhood exposure to traumatic events is associated with increased risk for psychosis (Holtzman et al., 2012, 2013; Varese et al., 2012). Among the childhood traumas that have shown the most consistent link are physical and sexual abuse. These are elevated in the histories of both diagnosed patients, and individuals who meet

clinical-high-risk criteria for psychosis (Holtzman et al., 2012). One question raised by these findings is whether they reflect causal effects of trauma versus evocative effects of the behavioral syndrome associated with vulnerability; in other words, the likelihood of being in situations that are linked with abuse may be greater for children at-risk for psychosis. Evidence supporting a causal effect comes from a study of patients, their healthy siblings, and unrelated controls (Heins et al., 2011). Discordance in psychotic illness across related individuals was predicted by differential exposure to trauma. The association between trauma and psychosis was apparent in a dose-response fashion across varying levels of illness and vulnerability to psychosis. Along these same lines, using the MZ-twin differences approach, data on childhood adversity and subclinical psychotic experiences were obtained from both twin-pairs members (Alemany et al., 2012). The investigators found that within-pair twin differences in exposure to childhood adversity were associated with corresponding differences in subclinical positive symptoms, suggesting that the relation between childhood adversity and symptoms is not solely attributable to heritable genetic differences in behaviors that evoke more adverse experiences.

Cross sectional studies of general life-event stress and daily stress exposure have not yielded consistent evidence that patients with psychosis or clinical-high-risk individuals are exposed to more stress (Holtzman et al., 2012). But the evidence is more consistent in demonstrating that both psychotic patients and clinical-high-risk individuals do report greater subjective stress in response to events. Further, longitudinal research suggests that the rate of stressful events is higher prior to the onset of psychotic episodes (Collip et al., 2011).

In considering the effects of trauma and stress on subsequent risk for psychosis, it is also relevant to note the evidence for stress sensitization, a phenomena in which exposure to stress enhances latter sensitivity to stress. Using the experience sampling method, one study of psychotic patients revealed that a childhood history of trauma was associated with increased stress reactivity later in life (Lardinois et al., 2011). Research on rodents has elucidated the neurobiological mediators for stress-sensitization. Repeated early stress exposure is associated with later increases in stress hormone and DA secretion in response to stressful events (Hall et al., 1999; Tidey & Miczek, 1996). Similar effects have been observed in humans with previous exposures to stressful events (Laruelle, 2000: Pruessner et al., 2004). The potential neurobiological substrate for stress effects and stress sensitization in psychosis will now be discussed in greater detail.

DEVELOPMENTAL STAGES IN THE EMERGENCE OF PSYCHOSIS

Premorbid Childhood Development

As mentioned previously, it is well documented that, on average, children who later develop a psychotic disorder manifest deficits in cognitive, motor, and social functions. Reviews of the retrospective and prospective research literatures on academic performance indicate that those who later develop schizophrenia performed below their sibling and peers beginning early in elementary school (Watt, Grubb, & Erlenmeyer-Kimling, 1982). Similarly, when compared with peers and siblings with healthy adult outcomes, those who later manifest psychosis show poorer performance on standardized intelligence tests (Aylward et al., 1984; Watt, Grubb, & Erlenmeyer-Kimling, 1982). Thus the cognitive impairment that is so often associated with serious mental illness can be observed long before psychosis onset.

In the domain of social function, there are also significant differences between children who develop psychosis in early adulthood and those who do not. Evidence to support this comes from prospective cohort studies as well as retrospective studies of diagnosed adult patients (Walker et al., 1993; Watt, Grubb, & Erlenmeyer-Kimling, 1982). Among the abnormalities observed by teachers and parents are increased social withdrawal and behavioral noncompliance, and studies of childhood home movies have revealed a lower rate of positive facial expressions of emotion.

Perhaps more than any other indicator, childhood deficits in motor function suggest a neurological basis for premorbid impairment. There is evidence of both abnormalities in movement and delays in motor development during infancy and childhood in individuals who subsequently develop psychotic disorders (Dickson, Laurens, Cullen, & Hodgins, 2012). Several studies have shown that within the first two years of life, individuals who later develop schizophrenia manifest delays and abnormalities in motor development (Fish, Marcus, Hans, & Auerbach, 1993; Walker, Savoie, & Davis, 1994). They are slower to acquire coordinated patterns of crawling, walking, and bimanual manipulation. They also show asymmetries and abnormalities in their movements, such as abnormal postures and involuntary movements of the hands and arms. It is important to note, however, that these early motor signs are not specific to schizophrenia or psychosis in general. Delays and anomalies in motor development are present in children who later manifest a variety of disorders, as well as some who show no subsequent disorder; thus, motor signs are not diagnostic. But the presence of motor deficits in

infants who subsequently manifest schizophrenia suggests that the congenital vulnerability to the disorder can involve brain systems that play a role in movement. In particular, subcortical regions of the brain, especially the striatum, play an important role in motor functions across the life span. The hyperkinetic nature of the motor abnormalities that have been observed in children prior to psychosis onset have been linked with increased dopamine (DA) activity in this region (Walker, 1994). Recent studies have shown that clinical-high-risk individuals and patients with psychosis have heightened DA activity in the striatum (Mizrahi et al., 2012; Wong et al., 1986).

Taken together, the results from research on childhood premorbid development indicate that vulnerability can be subtly expressed long before the onset of clinical psychosis. On the other hand, when considering the research findings it is important to keep in mind that there is variability in premorbid adjustment and it is possible that the variability maps onto differences in etiology (Walker et al., 1996).

The Prodromal Phase and Clinical High Risk

As mentioned already, prior to the onset of the clinical syndrome of schizophrenia and other psychotic disorders, there is typically a period of functional decline and gradual emergence of symptoms (Addington & Heinssen, 2012; Cannon et al., 2008; Holtzman et al., 2013). This *prodromal* period usually appears during adolescence and is the transitional stage from the premorbid state to the point at which the patient meets criteria for clinical psychosis. With respect to functional impairment, there is often a decline in academic and work performance, decreased interest in social and recreational activities, and problems with memory and concentration.

A range of symptoms is associated with the prodromal period, and the symptom pattern and sequence of emergence of symptom subtypes varies among patients (Neumann et al., 1995; Yung & McGorry, 1996). Among the symptoms that begin to manifest themselves earliest in the prodrome are mood changes, and many patients with psychotic disorders are diagnosed with depression before they have psychotic symptoms (Fusar-Poli et al. 2012). Positive symptoms, which are the defining feature of prodromal syndromes using prospective criteria, initially present in an attenuated form (Cannon et al., 2008). For example the individual might report unusual perceptual experiences, such as hearing voices when no one else is around or seeing some an unidentifiable object out of the corner of his eye. In the prodrome, such experiences are attributed by the individual to imagination or error, thus lacking the conviction that is typically shown in patients who meet *DSM* criteria for hallucinations. In fact, these psychotic-like symptoms increase in frequency through the course of normal adolescence and diminish for most by early adulthood (Kelleher & Cannon, 2011). But for those who eventually develop a psychotic disorder, the unusual sensory experiences and ideas become more compelling, and eventually the individual is convinced they are real. When this threshold of conviction is crossed and the symptoms persist, the individual is likely to meet the diagnostic criteria for a psychotic disorder. If there are accompanying symptoms of mood disorder, such as depression or mania, the individual may meet criteria for a diagnosis of schizoaffective disorder or major depression with psychotic features

As mentioned, the prodromal phase has been the subject of increasing research interest because it may be the optimal period for identifying neuropathological processes and, ultimately, for preventive intervention. While the initial research on the prodrome relied on retrospective data obtained from diagnosed patients, investigators are now studying the prodrome prospectively by utilizing assessments aimed at measuring the presence and severity of 'prodromal' signs. Several structured approaches for prospective assessment of prodromal syndromes have been developed and are currently being used in longitudinal studies (Addington & Heinssen, 2012; Correll et al., 2010). These measures focus on *subclinical* manifestations of the perceptual, ideational, and behavioral symptoms of psychosis. In the research literature, individuals who manifest symptoms that meet predetermined severity and duration criteria are designated as clinical-high-risk, ultra-high risk, or prodromal. Because the term prodromal may be taken to imply the inevitability of a subsequent illness, most in the field use the term clinical-high-risk (CHR) to refer to individuals who are manifesting putative prodromal syndromes.

In the United States, the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003) has been the most widely used measure. Like other prodrome assessment tools, it rates the presence and severity of subclinical positive (e g, suspiciousness, unusual ideas and perceptual experiences) and negative (e.g., social withdrawal, decreased emotional expression and role functioning) symptoms, as well as mood and vegetative symptoms. Based on SIPS ratings, individuals who meet CHR criteria can manifest several different syndromes, most often an attenuated positive symptom syndrome or schizotypal personality disorder. Using such measures to identify

CHR samples enhances positive predictive power above the population prevalence rate, as well as the risk rate for first-degree relatives of psychosis patients of about 12% (Sorensen et al., 2009). It has been estimated that 20–40% of CHR individuals will transition or convert (i.e., meet criteria for a psychotic illness) within a roughly 2-year period (McFarlane, 2011), a rate much higher than that of the general population (Eaton, 1999). While the CHR state is sometimes thought of as the 'psychosis prodrome,' conversions to affective illnesses are common, reflecting overlapping developmental trajectories across psychotic illnesses (O'Donovan, Craddock, & Owen, 2009).

The CHR period may be a unique window of opportunity for preventive interventions (Correll, Hauser, Auther, & Cornblatt, 2010). But the opportunities for intervention will be enhanced when current prediction algorithms are refined so that predictive power (sensitivity and specificity) is increased and false positives levels are reduced. Currently ongoing prospective CHR studies are aimed at boosting predictive power (Addington & Heinssen, 2012; Cannon et al., 2008). In addition, these studies are concerned with elucidating neural mechanisms involved in the emergence of psychosis. The North American Prodrome Longitudinal Study (NAPLS) project is the largest investigation of this kind in the United States, and is comprehensively tracking biobehavioral development in CHR individuals (Cannon et al., 2008).

It should be emphasized that, in addition to their elevated risk for psychotic illness, CHR individuals experience significant cognitive dysfunction, distress, and difficulties with social and occupational functioning, and they are often treatment-seeking (Addington & Heinssen, 2012). Cognitive deficits are found in several areas, including attention, planning, and processing speed (Seidman, 2006), and these deficits are most pronounced in those who later transition to psychosis. Similarly, CHR youth score below healthy controls on measures of social-cognitive skills (Fusar-Poli et al., 2012; Thompson, Bartholomeusz, & Yung, 2011). As in the premorbid childhood period, motor abnormalities have also been detected in adolescents who manifest CHR syndromes, including schizotypal personality disorder. Specifically, compared with healthy adolescents, CHR youth show more involuntary movements and coordination problems (Nagy & Szatmari, 1986; Walker et al., 1999). In the area of social functioning, CHR youth often report growing isolation from friends and family, increased conflict with others, the inability to forge new friendships, and a lack of interest in social contact (Cornblatt et al., 2007). Finally, CHR individuals report increasing distress stemming from their inability to think clearly, declining functioning, and attenuated positive symptoms.

To date, longitudinal studies of CHR youth have also yielded a number of behavioral predictors of conversion to psychosis. Among these are greater cognitive impairment, functional deficits, and motor abnormalities (Addington & Heinssen, 2011; Mittal & Walker, 2007; Mittal et al., 2008). More recently, investigators have begun to identify biological markers of risk for transition in CHR populations. These are discussed as we explore the neurochemical and brain abnormalities associated with psychosis.

NEUROBIOLOGICAL MECHANISMS

Inflammatory Processes and Oxidative Stress

As mentioned, there is evidence that risk of subsequent schizophrenia is heightened by fetal exposure to maternal infection. These and other findings have stimulated interest in the potential role of inflammatory processes in psychosis. Recent evidence suggests that neuroinflammation may be involved in both conferring vulnerability and triggering illness expression (Miller et al., 2011). By way of background, the key elements of inflammatory processes will be summarized.

Inflammation, a complex cascade of biological responses, is controlled by immune cells and cytokines. Immune cells (B-cells, T-cells, and phagocytes) act to fight infection. B-cells act via the secretion of antibodies that attack antigens, whereas T-cells act more directly to attack infected cells and also regulate immune responses. Cytokines are immunomodulating substances that are secreted by cells of the immune system. They are proteins, peptides, or glycoproteins that act as signaling molecules in communication among cells. They are secreted in response to immunological challenges, such as exposure to infection. Some cytokines are proinflammatory (interleukin-1 and tumor necrosis factor—alpha [TNF-α]) and serve to initiate an inflammatory response and activate phagocytotic cells to combat infection. However, excessive inflammation can exacerbate or trigger diseases. Thus, other cytokines are anti-inflammatory (e.g., transforming growth factor beta [TGF-β], Interleukin-4, Interleukin-10, Interleukin-11, and) and serve to reduce inflammation and promote healing, and can be neurotrophic. Numerous cytokines are found in the brain, where they play important signaling roles, in addition to their immunological functions. Cytokines have many targets, including immune cells, neurons, and astrocytes. Their actions on neurons are

not completely understood, but they are known to have both neuroprotective and neurotoxic properties.

A substantive body of research supports a role for inflammatory processes and oxidative stress in psychosis. Inflammatory markers are elevated in blood, brain, and CSF in first episode and chronic patients with psychosis (Bechter et al., 2010; Maxeiner et al., 2009; Miller et al., 2011; Potvin et al., 2008). However, several physical and behavioral characteristics that are more common in patients, such as obesity and smoking, affect levels of these cytokines and complicate inferences regarding the role they play in psychosis (Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011). As such, cytokines that are elevated in individuals in their first episode of psychosis and which track with symptom levels are of greatest interest, as they are less likely to be a byproduct of chronic psychosis and related factors: these include IL-6 and transforming growth factor-beta (TGF- β), which is typically anti-inflammatory (Miller et al., 2011)**.** As might be expected, antipsychotics have been shown to normalize cytokine functioning (Zhang et al., 2004), symptoms have been shown track with changes in cytokine levels**,** and some studies have found that cytokines can be used to predict responsivity to antipsychotic treatment (Xiang Yang Zhang, Zhou, Cao, Wu, & Shen, 2005).

A diffusion tensor imaging (DTI) measure of extracellular volume (free water), an indirect index of neuroinflammation, showed that first-episode schizophrenia patients have elevated free water volume, indicating the involvement of regionalized neuroinflammation in early psychosis (Pasternak et al., 2012). In vivo human PET imaging studies find elevations of activated microglia, another hallmark of neuroinflammation, in persons with schizophrenia (Doorduin, de Vries, Willemsen, de Groot, Dierckx & Klein, 2009; van Berckel, et al., 2008). Microglia are now understood to be involved in normal regulation of synaptic plasticity and directly participate in pruning at glutamatergic synapses by phagocytizing less active synapses (Schafer, Lehrman & Stevens, 2012).

Related to this, research also suggests a role for oxidative stress in psychosis. The term *oxidative stress* refers to an imbalance between a biological system's chemically reactive molecules containing oxygen (i.e., reactive oxygen species) and its ability to 'detoxify' the reactive intermediates or to repair the resulting damage. When oxidants and antioxidants are imbalanced in favor of the oxidants, disturbances in the normal redox state of cells can result in toxic effects that damage the cells, including their DNA and signaling capacity. Oxidative stress is elevated during inflammation as part of the host response and can remain elevated under chronic stress (Schiavone, Jaquet, Trabace, & Krause, 2013). Failure of the body's antioxidant defense system to control oxidative stress results in damage to cells that can, in turn, increase the inflammatory response. As with inflammation, markers of oxidative stress are higher in schizophrenia patients (Yao & Keshavan, 2011).

Further evidence that inflammation and oxidative stress are clinically relevant to psychosis is found in several small placebo controlled clinical trials reporting that anti-inflammatory drugs (Laan et al., 2010; Levkovitz et al., 2010; Muller et al., 2002, 2004; Rapaport et al., 2005) and the antioxidant precursor *n-acetyl-cysteine* (Carmeli, Knyazeva, Cuenod, & Do, 2012) used adjunctively with antipsychotic medications ameliorate residual symptoms. Results from a population-based case-control indicated a 60% reduction in psychosis risk in male chronic NSAID (Nonsteroidal anti-inflammatory drugs) users (Laan et al., 2007).

It is well documented that stress and inflammatory processes are inter-related, and that stress exposure can increase susceptibility to infection (Frank, Thompson, Watkins, & Maier, 2012). In the following section we examine biological aspects of stress and evidence that suggests how it might be implicated in psychosis via several pathways, including inflammation.

Stress Biology

As described previously, there is an extensive body of literature documenting the association between stress exposure and risk for psychosis. Investigators are now exploring the neurobiological processes that mediate this association. Among the brain systems that mediate the mammalian response to stress is the hypothalamic-pituitary-adrenal (HPA) axis.

The response of the HPA axis to stress entails a cascade of neurohormonal signaling (Armario et al., 2012; Danese & McEwen, 2012; Hill & Tasker, 2012; Jameison & Dinan, 2001; Stevens & White, 2010). Following stress exposure, cortical input to corticotrophin-releasing hormone (CRH) neurons in the periventricular nucleus (PVN) of the hypothalamus results in the release of CRH from neuronal axon terminals into pituitary circulation. CRH then stimulates secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland into the bloodstream. ACTH, in turn, stimulates adrenal gland production of glucocorticoids (principally cortisol in primates and corticosterone in rodents) via type 2 melanocortin receptors (MC2-R), thereby initiating synthesis of cortisol which is released into circulation. Glucocorticoids act on tissue

throughout the body and cross the blood–brain barrier to act on multiple brain regions via both membrane and intracellular receptors on neurons. Homeostasis in the system is achieved, in part, through negative feedback via receptors for glucocorticoids (GRs) that are located throughout the brain; direct modulatory feedback is provided by hypothalamic and pituitary GRs, while indirect modulation is provided by limbic, thalamic, and frontal cortex GRs. Another receptor that binds glucocorticoids is the mineralocorticoid receptor (MR). Like GRs, MRs are located in many brain regions and also play a role in modulation of the HPA axis.

In the absence of stress, the majority of MRs are occupied, while only about 10% of GRs are bound to glucocorticoids. However, during stress or at the peak of the diurnal cortisol rhythm (i.e., morning), MRs are saturated and higher proportions of GRs become occupied (Silverman & Sternberg, 2012; Stevens & White, 2010). Both animal and human studies suggest that the relative proportion of MR to GR activation may be an important moderating factor in multiple brain processes, with the relation of the ratio of activation to brain function constituting an inverted U such that too much or too little can impair cognitive functions (de Kloet et al., 1999; Lupien et al., 2002).

In response to persistent stress exposure, the HPA axis changes at multiple levels, and while this has primarily been documented in experimental animal research, there is evidence that similar processes occur in humans. For instance, chronic elevations in ACTH can contribute to adrenal hyperplasia in humans, which can result in greater cortisol output in response to the same level of ACTH (Harvey & Sutcliff, 2010; Oitzl et al., 2010). There are also changes at the level of the pituitary that may contribute to alterations in the set point of the HPA axis (Danese & McEwen, 2012; Krishnamurthy et al., 2012; Mondelli et al., 2008). Finally, changes in the negative feedback at multiple levels can result from glucocorticoid-induced compromises to brain structure (Damstead et al., 2011).

Chronic glucocorticoid exposure appears to have adverse effects on numerous brain regions. Sustained corticosterone elevations in rodents, including those due to chronic stress or corticosterone administration, are associated with the regression of synapses and a decrease in dendritic spines in hippocampal and prefrontal neurons (for reviews, see Bennett, 2008; Damstead et al., 2011; McEwen, 2012). Also, elevated glucocorticoids can affect calcium ion channels, structural protein levels in glial cells, and amino acid levels in the hippocampus, and suppress myelination of neuronal processes, an important aspect of adolescent brain development that is related to regional volumetric changes (Belanoff et al., 2001; Damstead et al., 2011). Moreover, in rodent and primate hippocampus, persistent stress and glucocorticoid elevations lead to reduced neuronal excitability (Joels, 2001), impaired synaptic plasticity (McEwen, 2012), and reduced neurogenesis (Schoenfeld & Gould, 2012). The association in humans of increased cortisol levels with decreased hippocampal (Tessner et al., 2007) and cortical gray matter volume (Mainz et al., 2012) is consistent with these findings.

HPA activation is, of course, only one mediator of the biological stress response. Its activation trails the more rapid response by the sympathetic–adrenal–medullary (SAM) axis within the sympathetic nervous system which involves stimulation of catecholamine release (Chrousos, 2009). Prefrontal cortex and limbic structures also contribute to the regulation of SAM function in response to stress.

The present discussion focuses primarily on the role of the HPA axis in mediating the stress response because it has received greater attention in research on psychosis. This is partially a consequence of the ease of measuring secretagogues involved in HPA function, especially cortisol, which can be assayed noninvasively and reliably in saliva (Walker et al., 2008). Further, research has revealed pervasive effects of glucocorticoids on brain structure and function, including hippocampal abnormalities that have been shown to be linked with psychosis (Mondelli et al., 2010). HPA function can, of course, be indexed in secretagogues other than cortisol, including via measurement of ACTH (Stevens & White, 2010). Compared with cortisol, however, ACTH has been relatively neglected in research on psychosis.

In addition to affecting neuronal morphology, glucocorticoids interact with and modulate neurotransmitter systems in the brain, so their effects on brain function and circuitry can be pervasive (McEwen, 2012). For example, HPA axis activation, as indexed by heightened levels of cortisol, leads to the augmentation of DA levels in the human brain (Wand et al., 2007). This is particularly relevant for psychosis because DA, more than any other neurotransmitter system, is implicated in the full spectrum of psychotic disorders (Howes & Kapur, 2009). Animal models indicate that glucocorticoid levels also affect serotonin (Belanoff et al., 2001; Heim & Binder, 2011), norepinephrine (Rastogi & Singhal, 2012), and glutamate in the cortex (Wolf, 2003; Bennett, 2008).

It is important to note the normative developmental augmentation in activation of the HPA axis in humans, as this augmentation parallels the gradual age-related increase in risk for psychotic disorders. Specifically, there is a postpubertal increase in basal and stress-induced cortisol

secretion that occurs in conjunction with advancing stages of puberty and appears to extend into the 3rd decade of life in humans (Adam, 2006; Lupien et al., 2002; Shirtcliff et al., 2011; Walker et al., 2010). This maturational increase in activity has been hypothesized to heighten stress sensitivity in adolescence (Eiland & Romeo, 2012; Walker et al., 2008). To date, we are aware of no published studies on adolescent maturational changes in other indices of HPA function in humans, thus more research is needed to elucidate changes in CRH, ACTH, and other secretagogues. Such investigations are especially important in light of the evidence that HPA activity is involved in the expression of vulnerability for psychosis.

The immune system and stress are intricately interrelated. Activation of the immune system and the HPA axis appear to be mutually mediated and synergistic and, if persistent, are linked with similar neurochemical and neuroanatomical changes (Zunszain et al., 2011) and impaired long-term potentiation (LTP), i.e., the neuronal changes that mediate learning (Kim & Haller, 2007; Yirmiya & Goshen, 2011). Although glucocorticoids have anti-inflammatory effects at low/moderate levels, exposure to persistent stress or glucocorticoid administration can increase the pro-inflammatory response to an immune challenge (Catena-Dell'Osso et al., 2011; Frank MG, Miguel ZD, Watkins LR, Maier, 2010). Glucocorticoids also sensitize the proinflammatory microglia response, thereby priming microglia to respond excessively to immune challenge (Frank, Thompson, Watkins & Maier, 2012). Conversely, activation of the immune response can augment HPA activity, via cytokines (Frank, Miguel, Watkins & Maier, 2009).

There is a burgeoning literature on the relation between the HPA axis and psychosis. In a review, Walker et al. (2008) summarized several trends in the research findings that support the assumption that activation of the HPA axis can trigger the expression of vulnerability for psychosis, and subsequent research findings have converged on the same conclusions (Holtzman et al., 2012, 2013). First, there is evidence that patients with psychosis, especially non-medicated patients, have higher baseline cortisol levels, and studies published subsequent to the review by Walker and colleagues (2008) provided additional support for this conclusion (Borges, Gayer-Anderson, & Mondelli, 2013; Garner et al., 2010; Kale et al., 2010; Venkatasubramanian et al., 2010). Although there are fewer studies of ACTH, largely due to limitations on its assay in saliva and urine, there is also evidence of elevated ACTH in psychotic patients (Brunelin et al., 2008; Ryan et al., 2004). ACTH and the DA metabolite homovanillic acid (HVA) response to metabolic stressors are also elevated in psychotic patients relative to controls (Brunelin et al., 2008). Moreover, a recent postmortem study of pituitary glands from schizophrenia patients and controls revealed that the level of ACTH was elevated (Krishnamurthy et al., 2012).

Second, antipsychotic medications, and many antidepressants, reduce cortisol and ACTH secretion, in addition to decreasing positive symptoms, and findings published subsequent to the aforementioned review support this effect as well (Venkatasubramanian et al., 2010). Similarly, drugs that are direct cortisol antagonists have been shown to decrease psychotic symptomatology in mood disorders and Cushing's disease (Schatzberg & Lindley, 2008).

Third, psychotic patients show HPA axis dysfunction in response to pharmacologic challenge, such as the DEX suppression test (DST). For example, administration of DEX, an exogenous glucocorticoid, typically leads to cortisol suppression due to the HPA axis negative feedback loop. DEX binds to GRs that, in turn, inhibit the secretion of ACTH and cortisol. Thus, cortisol nonsuppression after the DST is an index of HPA axis dysfunction. In the DEX/CRH test, a more sensitive measure of HPA function, DEX is administered, then the following day CRH is administered, and ACTH and cortisol responses are measured. More pronounced ACTH and cortisol secretion in response to CRH reflect reduced glucocorticoid feedback regulation. The previous review by Walker and colleagues (2008) and other reports (Owashi et al., 2008) have found higher post DST and DEX/CRH levels of cortisol and ACTH in patients with schizophrenia and affective psychoses than in healthy and depressed comparison groups. In many patients, this response is reversible with antipsychotic treatment (Ceskova et al., 2006).

Fourth, neuroimaging studies of psychosis patients have consistently revealed volumetric reductions in brain regions that are sensitive to heightened cortisol. It is noteworthy that comparisons of discordant MZ twins suggest that among the most pronounced reductions are those in the hippocampus (Shepherd et al., 2012). Given the role of the hippocampus in modulating HPA activation, these results are also consistent with reports of an inverse correlation between baseline cortisol and hippocampal volume in psychosis (Mondelli et al., 2012).

Fifth, the severity of most symptom dimensions, including positive, negative, and mood symptoms, tend to be positively related to cortisol levels in samples of patients with psychosis. Recent studies of first-episode psychotic patients revealed significant associations of positive and negative symptom severity with cortisol levels (Belvederi Murri et al., 2012; Garner et al., 2012). Further, the

magnitude of symptom severity reduction in response to antipsychotic medications has been linked with the magnitude of cortisol decrease (Mondelli et al., 2012).

Finally, a causal role for HPA activity in triggering or exacerbating psychotic symptoms is supported by research on hypercortisolemia. For example, hypercortisolemia induced by administration of exogenous corticosteroids in high doses can trigger psychotic symptoms (Buchman, 2001; Warrington & Bostwick, 2006). Symptoms of hypercortisolemia-induced psychosis include pressured speech, hallucinations, delusions, and disorganized thought, which are often indistinguishable from the symptoms of psychotic disorders (Ling et al., 1981; Lewis & Smith, 1983; Wada et al., 2001). Indeed, disorders characterized by hypercortisolemia, such as Cushing's syndrome, often involve psychotic symptoms that remit in conjunction with normalization of cortisol levels in response to treatments such as etomidate, an adrenal suppressant (Chan et al., 2011), mifepristone (van der Lely et al., 1991; Chu et al., 2001), and other treatments (Kelly et al., 2003). Interestingly, the risk for psychotic symptoms in Cushing's, though elevated across the life span, is lower in childhood than in young adulthood.

Although there is relatively consistent evidence for elevated baseline cortisol secretion in psychosis, especially in nonmedicated patients, the results of investigations of psychosocial stress-induced cortisol are mixed. Some studies using laboratory psychosocial stressors have found that psychotic patients show no difference or less cortisol increase after stress induction, both on (Jansen et al., 2000; Brenner et al., 2009) and off (van Venrooij et al., 2012) antipsychotic medications. The absence of an enhanced psychosocial stress-induced cortisol increase in psychosis, despite evidence for baseline elevations, may reflect several factors. First, there may be ceiling effects on cortisol increments beyond heightened baseline levels (Crowley et al., 1993). Second, after the onset of psychosis, the stress generated by the symptoms, especially distressing perceptions and ideations, may be more subjectively salient than the effect of any external psychosocial stress. Moreover, the psychosocial events that have the capacity for generating stress may be more idiosyncratic for psychotic patients than for healthy individuals. As discussed earlier, psychosis patients subjectively experience daily events as more distressing than healthy controls, even in the absence of increased stressor frequency.

HPA axis abnormalities, including elevated cortisol levels, have also been found in individuals at increased risk of psychotic illness (Aiello, Horowitz, Hepgul, Pariante, & Mondelli, 2012). In both CHR and genetic high-risk samples, higher cortisol levels are associated with increased risk for psychosis and severity of psychotic symptomatology (Mittal et al., 2013; Walker, Mittal, & Tessner, 2008). A recent report from the NAPLS project on the prodrome to psychosis revealed that CHR youth manifested higher baseline cortisol than matched controls (Walker et al., 2013). Further, among the CHR group, those who transitioned to psychosis showed the highest baseline cortisol level. It is possible that elevated cortisol may be is especially important in the early development of psychotic illness, as it is known to be involved in neurodevelopmental processes, such as synaptic pruning, whose dysregulation is associated with psychotic illness (Cannon, 2008).

Another biological system that is linked with both the inflammatory response and HPA activity is the gut microbiome, the microorganisms that reside in the digestive system. There is recent evidence that psychotic patients manifest abnormalities in the microbiome (Yolken, 2013). Recent experimental research with animals has shown links among HPA activity, cytokines, and the gut microbiome (Cryan & Dinan, 2012). For example, maternal separation in rhesus monkeys results in increased HPA activity (O'Mahony, Hyland, Dinan, & Cryan, 2011) and changes in fecal lactobacilli levels (Bailey & Coe, 1999). Similar effects have been demonstrated in murine models: chronic stress in adult mice has been shown to affect HPA activity, microbiota composition, and inflammatory cytokines (Bailey et al., 2011; O'Mahony et al., 2009). Consistent with the results from animal models, stress exposure in humans is associated with disruption of the intestinal barrier, increases in circulating levels of inflammatory cytokines and HPA activity, and a predisposition toward depression (Maes, Kubera, Leunis, & Berk, 2012). Further, in humans, probiotics have shown promise in the treatment of psychiatric symptoms (Messaoudi et al., 2011; Tillisch et al., 2012).

In summary, there is now extensive evidence at the biological level supporting the validity of the longstanding assumption that stress plays a role in psychotic disorders. Further, the HPA axis and the immune system are closely linked, and both are associated with structural brain characteristics. This raises the possibility that interventions targeting these systems may be effective in the treatment of the neuropathology underlying psychosis (Cohen et al., 2012).

Structural and Functional Brain Abnormalities

Since the inception of neuroimaging, our understanding of the brain abnormalities in psychosis has burgeoned. Structural brain imaging, predominantly magnetic resonance

imaging (MRI), has revealed significant mean reductions in the volume of several brain regions in patients with psychotic disorders when compared with healthy controls. These include gray matter reductions of the anterior cingulate, frontal (particularly medial and inferior) and temporal lobes, hippocampus, amygdala, thalamus, and insula (Shephard et al., 2012). Longitudinal studies indicate that there are also changes over the course of the illness. A meta-analysis showed the greatest volume loss over time is in total cortical gray matter, most notably the left superior temporal gyrus, left anterior gyrus, left Heschl gyrus, left planum temporal, and posterior superior temporal gyrus bilaterally (Vita et al., 2012). The volumetric declines in gray matter appear to be especially pronounced early in the disease process; relative to healthy controls, first-episode patients showed greater progressive decline in cerebral gray matter volume, including frontal, temporal and parietal lobes, and left Heschl gyrus. Although not as pronounced, there is also evidence of white matter volume reductions in both affective and nonaffective psychotic disorders (De Peri et al., 2012).

While the causes of these volumetric decreases are unknown, and they are observed prior to the provision of treatment, there is some evidence from naturalistic studies of patients treated with antipsychotics that declines during the course of illness are partially linked with duration and dosage of antipsychotic medication (Fusar-Poli et al., 2013). The latter evidence is not based on controlled clinical trials; however, Fuser-Poli and colleagues (2013) noted findings from experimental animal studies indicating that antipsychotic exposure is linked with brain volume decline. Clearly further research is needed to address the effects of antipsychotics on brain structure, yet it has become apparent from studies of CHR samples that brain volume decline precedes both the onset of psychosis and the initiation of treatment.

A meta-analysis of research findings from studies of CHR samples compared with matched controls showed significant reductions in gray matter volume in the right superior temporal gyrus, left precuneus, left medial frontal gyrus, right middle frontal gyrus, bilateral parahippocampal/hippocampal regions and bilateral anterior cingulate (Fusar-Poli et al., 2011). The CHR individuals who transitioned to a psychotic episode showed more pronounced baseline gray matter volume reductions in the right inferior frontal gyrus and in the right superior temporal gyrus. These findings have been replicated subsequent to this meta-analysis. In a longitudinal study of 102 CHR participants, 28 of whom developed psychosis (19 schizophrenia, 7 affective psychoses, and 2 other psychoses) subsequent to scanning, those in the CHR sample who developed psychosis (schizophrenia and affective psychosis) showed baseline reductions in the frontal cortex relative to those who did not (Dazzan et al., 2012). The subgroup that transitioned to schizophrenia also showed smaller volumes in the parietal and temporal cortices, and those with affective psychosis had significantly smaller subgenual cingulate volumes. Similar findings have been reported for individuals at genetic high-risk (i.e., first-degree relatives of diagnosed patients) when followed longitudinally; the genetic high-risk group had significantly greater reductions over time than the control group for whole brain volume and left and right prefrontal and temporal lobes (McIntosh et al., 2011). Among the high-risk participants, those who later showed psychotic symptoms manifested greater prefrontal reductions than those who did not. In summary, it appears that brain volumetric reductions precede the onset of psychosis and are not a consequence of the illness.

Inflammatory processes and oxidative stress may be involved in the brain abnormalities observed in patients suffering from psychotic disorder. Inflammation is associated with gray matter volume loss and dysregulated synaptic plasticity. Several studies indicate that chronic neuroinflammation (Frodl & Amico 2013; Mondelli et al., 2011) and reduced endogenous antioxidants (Fraguas et al., 2012) are associated with gray matter loss in schizophrenia and other brain disorders. Interestingly, recent studies in early psychosis patients suggest that anti-inflammatory interventions may attenuate progressive brain changes (Meyer, 2013). It is possible that regionalized excessive synaptic pruning by activated microglia, the hallmark of neuroinflammation, may contribute to gray matter reductions occurring at the onset of psychosis.

Of course, many neurological disorders are associated with reduced brain volume, so the previous findings have not led investigators to implicate a specific brain region in the etiology of psychosis. Instead, it is now generally assumed that these gross anatomical differences are nonspecific indicators of a neuropathological process, and that the critical substrate for psychotic disorders entails an abnormality in neural circuitry (Lisman et al., 2008). Using diffusion tensor imaging (DTI) and functional MRI (fMRI), investigators are beginning to examine circuitry function in psychotic disorders. (Fitzsimmons, Kubicki & Shenton, 2013).

Due to the complexity of the human brain, locating abnormalities in a segment of any one of the many circuits traversing the brain is a challenging task. Not only are there multiple segments in each circuit, but they entail different neuronal subtypes and neurotransmitters. Thus

there are multiple ways the function of any one circuit can be disrupted. A review of the research findings concerning the molecular aspects of circuitry dysfunction in psychosis is beyond the scope of this chapter, but some recent scientific developments are noteworthy. These findings have highlighted the longstanding assumption that DA is involved in psychotic symptom expression.

The notion that DA is involved in the emergence of psychotic symptoms, especially positive symptoms emerged from two established findings (Kuepper, Skinbjerg, & Abi-Dargham, 2013). First, all of the medications that have been found to be effective in the treatment of psychosis share the capacity to antagonize DA activity, primarily by blocking receptors. Second, agents that heighten DA activity in the brain also have the potential to trigger or exacerbate psychotic symptoms in some individuals. For example, amphetamine use can induce psychotic symptoms.

Adding to this evidence, research has demonstrated that brain DA activity, particularly in the striatum, is elevated in schizophrenia (Howes & Kapur, 2009). The striatum is a subcortical area comprised of the caudate, putamen, and nucleus accumbens. DA is a major neurotransmitter in the striatum and it is part of multiple cortico-striatal-thalamic circuits that subserve various cognitive and motor functions. A comprehensive overview of the research literature summarized the following replicated findings: using position emission tomography (PET) and single photon emission tomography (SPECT), investigators have shown there is 1) increased DA synthesis and release in striatal regions in medication-naive psychotic patients; 2) increased amphetamine-induced DA release, and 3) a subgroup of patients manifest increased DA receptors of the D2 subtype in the striatum (Kuepper, Skinbjerg, & Abi-Dargham, 2013).

A structural and functional distinction has been made between the ventral and dorsal striatum, although authors vary in how they make the distinction (Mathews et al., 2013; Voorn et al., 2004). The term ventral striatum is typically used to refer to the nucleus accumbens and the portions of the caudate and putamen below the internal capsule. It receives inputs from, and projects to, anterior cingulate, orbitofrontal, and anterior temporal cortices, as well as to hippocampus, insula, amygdala, and hypothalamus. Thus, it is the area of the striatum with primary connectivity with limbic structures (e.g., the amygdala, hippocampus, and thalamus) and is sometimes referred to as the mesolimbic system. The ventral striatum receives projections via DA fibers from the ventral tegmental area (VTA), known as the mesolimbic DA system. In contrast, the dorsal striatum is the larger area of the caudate and putamen above the internal capsule, and often referred to as the nigrostriatal pathway. Dorsal striatum projections arise from and lead to the frontal eye fields, premotor, supplementary, and primary motor cortices, and dorsolateral prefrontal, somatosensory, and parietal association cortices, regions involved in executive functions. DA input to the dorsal striatum arises primarily from the substantia nigra.

Although past theories had more often implicated the ventral striatum, or mesolimbic system, in psychosis, more recent evidence also implicates the dorsal striatum (Kuepper, Skinbjerg, & Abi-Dargham, 2013). The dorsal striatum plays a major role in motor functions, and it is well established that DA abnormalities in this region are linked with movement abnormalities (Walker et al., 1994). This area is also sometimes referred to as the associative striatum because 1) it appears to play a significant role in stimulus-response habit formation via input from sensorimotor cortex and 2) the dorsomedial area of the striatum, via cortical connections, is involved in the cognitive control of behavior (Liljeholm & O'Doherty, 2012). As discussed earlier, executive functions are among the most impaired in patients with psychotic disorders.

Consistent with the notion of increased DA activity in dorsal striatal circuitry, a recent MRI study examined brain responses to a cognitive task in psychotic patients and controls, and showed greater task-evoked hyperactivity of the substantia nigra of patients (Yoon et al., 2013). This occurred in association with changes in prefrontal and striatal activity in the psychotic group. The general pattern of results indicated that functional connectivity of the prefrontal cortex with these dysfunctional striatal regions was decreased in the patients.

As investigators have intensified their focus on DA function in CHR individuals, the findings converge with those from studies of diagnosed patients and implicate DA function in the dorsal striatum. Two studies found elevated dopamine synthesis in the dorsal striatum of CHR youth compared with healthy controls, and this was most pronounced in CHR youth who transitioned to psychosis (Egerton et al., 2013; Howes et al., 2011). Another PET study showed that higher synaptic DA concentration, measured globally in the striatum, was associated with more severe positive symptoms in CHR patients, and a greater reduction of these symptoms following DA depletion (Bloemen et al., 2013). Finally, providing a link between environmental factors and DA activity, both CHR individuals and schizophrenia patients were found to show greater stress-induced DA release in dorsal regions of the striatum, including the associative striatum (i.e., the predorsal putamen, predorsal and postdorsal

caudate) and the sensorimotor striatum (i.e., postdorsal putamen) when compared with healthy participants (Mizrahi et al., 2012). There was no group difference in DA in the ventral striatum. The emerging evidence of more pronounced DA activity in the dorsal striatum of CHR and psychotic patients is consistent with the findings of motor abnormalities in CHR youth.

In addition to DA, glutamate is another neurotransmitter that has been hypothesized to be linked with psychosis (Javitt, Zukin, Heresco-Levy, & Umbricht, 2012). This is based on evidence that agents that block *N*-methyl-D-aspartate-type (NMDA) glutamate receptors, such as ketamine, increase extracellular glutamate and also induce psychotic symptoms. Conversely, compounds that enhance NMDA receptor function (i.e., agonists) can reduce symptoms and improve cognition in schizophrenia patients. Using proton magnetic resonance spectroscopy ((1)H-MRS), it has been shown that both CHR and first-episode psychosis groups manifest higher levels of glutamate than controls in the dorsal-caudate (de la Fuente-Sandoval et al., 2011). The authors note that this is a DA-rich region implicated in the pathophysiology of psychosis, and that the findings are consistent with evidence that heightened glutamate is associated with an increase in DA release in the striatum. In another PET study of CHR subjects, there was a significant negative relationship between hippocampal glutamate levels and striatal DA synthesis, but this was not observed in controls (Stone et al., 2010). The authors speculate on the potential cascade of interactions among neurotransmitters that can lead to dysfunction of brain circuitry.

Like DA, glutamate activity is also influenced by glucocorticoids. Prolonged stress exposure or administration of glucocorticoids suppresses glutamatergic transmission by reduction of surface glutamate and synaptic NMDA receptors (Timmermans, 2013). This results in a decrease in synaptic plasticity and LTP, thus contributing to cognitive deficits. These and related findings have led to the speculation that prenatal exposure to infection and stress may set the stage for vulnerability to psychosis via sustained activation of immuno-inflammatory pathways and concomitant increases in microglia activation (Anderson & Maes, 2013). During postnatal development stress exposure would constitute a second challenge to inflammatory and oxidative stress pathways, triggering autoimmune and pro-inflammatory responses that lead to a cascade of neurotransmitter abnormalities, especially NMDA receptor hypofunction. At the structural level, the consequences can be neurotoxicity and reduced neurogenesis, myelination and neuroplasticity.

Because there are multiple potential pathways for disrupting any brain circuit, it is not surprising that a variety of brain and neurotransmitter abnormalities have been linked with psychotic disorders. Thus, the efficacy of treatments may vary among patients, and future research may yield findings that enhance our ability to target treatments based on symptom or biological indicators. In the meantime, the available treatments are usually administered without consideration of symptom or biological factors.

TREATMENT AND PREVENTIVE INTERVENTION

Over the past three decades, there have been some modest advances in the treatment of psychotic disorders. Although there are not yet treatments that produce complete remission, the quality of life for patients can be dramatically enhanced by a combination of medication and psychotherapeutic approaches. It is worth noting, however, that many people who suffer from psychotic disorders do not have access to treatment, so many patients do not benefit from the following advances.

For individuals experiencing a first episode of psychosis, stabilization with antipsychotic medication is the initial goal, then maintenance and rehabilitation (Miyamoto, Miyake, Jarskog, Fleischhacker, & Lieberman, 2012). Stabilization of symptoms is considered necessary to set the stage for the psychological interventions and rehabilitation aimed at reducing symptom severity and enhancing functioning. During the maintenance phase, the goal is to reduce residual symptoms and prevent relapse, while rehabilitation programs are directed at enhancing independent living skills.

Antipsychotic Medication

When antipsychotic medication was first introduced in the 1950s, it had a highly beneficial impact on the lives of patients with schizophrenia and other psychotic disorders because, for most, it reduced the severity of positive symptoms. As a result, many were able to leave inpatient care, sometimes after years of hospitalization. Chlorpromazine (Thorazine) was the first in a series of medications that are now referred to as the typical antipsychotics or neuroleptics (Miyamoto, Miyake, Jarskog, Fleischhacker, & Lieberman, 2012). Consistent with the DA hypothesis of psychosis, these medication acted by decreasing, or antagonizing, DA activity especially at the D2 type of DA receptor. But these 'first generation' antipsychotics had significant side effects, especially movement disorders, with tardive dyskinesia being the most severe.

In the late 1980s, a new generation of atypical antipsychotic medications with fewer motor side effects was introduced. These drugs also reduce DA neurotransmission, but in addition have an effect on other neurotransmitters, including serotonin and glutamate. Among the atypical antipsychotics are Risperdal (Risperidone), Zyprexa (Olanzapine), Seroquel (Quetiapine), Geodon (Ziprasidone), Abilify (Aripiprazole), and Clozaril (Clozapine). While still not producing complete symptoms remission, there is some evidence that atypical antipsychotics are more effective than first generation antipsychotics at preventing relapse in first-episode patients (Alvarez-Jimenez et al., 2011a). Clozaril has been found to be one of the most effective of the atypical antipsychotics, especially in treatment-resistant schizophrenia; however, it is not the first line of treatment due to significant side effects (e.g., agranulocytosis and seizures). The atypical antipsychotics are now usually the first approach in the treatment of psychosis, but a recent collaborative national study comparing typical and atypical antipsychotics did not reveal significant differences with regard to their ability to enhance patients' social functioning (Swartz et al., 2007). Thus, the relative advantages of the new generation of antipsychotics are limited in terms of long-term prognosis. Further, they have their own side effects, including increased risk of metabolic syndrome, weight gain/obesity, and new onset or worsening of diabetes mellitus (Newcomer, 2005). As might be expected, medication side effects are significant obstacles to treatment compliance. This is particularly problematic, as 60% of first-episode patients relapse after 1-year if they do not continue antipsychotic treatment, (Alvarez-Jimenez et al., 2011b).One approach to improving compliance is the administration of injectable, long-lasting (depot) antipsychotic medication. This has the advantages of ease of use for the patient and the fact that the clinician can monitor compliance. Injectable antipsychotics, when combined with psychosocial treatments, appear to be very effective in reducing relapse rates (Zhornitsky & Stip, 2012).

Some of the initial trials of preventive intervention with CHR individuals suggested that atypical antipsychotics may have the same preventive potential. In one study, CHR youth were randomly assigned to either low-dose Risperidone with cognitive therapy or to usual care alone (McGorry et al., 2002). After 6 months, the rate of conversion to psychosis was 9.7% for those receiving Risperidone and cognitive treatment, and 35.7% for usual care. For Risperidone-compliant patients, protection against progression extended for, on average, 6 months after cessation of drug treatment. In another randomized, placebo-controlled trial with CHR patients, Olanzapine, an atypical antipsychotic, or placebo was administered for eight weeks (Woods et al., 2003). Although both groups showed a decline in prodromal symptoms, analyses revealed that those on Olanzapine showed fewer and less severe symptoms. There were, however, problems with adverse side effects, and Olanzapine patients gained significantly more weight. Yet, despite these initial promising findings, subsequent follow-up studies have not yielded support for the preventive effects of antipsychotic medications in prodromal samples. Recent systematic reviews of this literature conclude that the severity of prodromal symptoms can be reduced and the onset of the first psychotic episode delayed by combining pharmacologic and psychological therapies, but extended follow-ups of CHR individuals treated with antipsychotics have not shown a significant reduction in transition to psychosis (Addington and Heinssen, 2012).

Given the significant false positive rate of current prospective measures of the prodrome (60–80%), antipsychotics are not considered an appropriate treatment; only a minority of those who meet standard criteria will actually develop a psychotic disorder, and too many would be subjected to side effects unnecessarily (Broome & Fusar-Poli, 2012). Moreover, the prodrome typically emerges in adolescence/early adulthood and we know relatively little about the long-term effects of antipsychotic medication on development. As a result, it is recommended that administering antipsychotic medications to CHR individuals, especially youth, should not be standard treatment (Addington and Heinssen, 2012). As our knowledge of the effects of psychotropic medication on adolescent growth and development increases we will be in a better position to weigh any adverse effects against potential benefits, both short-term and long-term. At the present time, individuals who meet CHR criteria are typically medicated with antidepressants because mood symptoms are so common (Walker et al., 2009). Clearly, there is a need for the development of effective treatments that do not risk significant side effects for CHR individuals (Haroun, Dunn, Haroun, & Cadenhead, 2005).

Psychosocial Treatments

Although antipsychotic medication is typically the first step in the treatment of psychotic disorders, there is now extensive evidence that psychosocial interventions are also beneficial for both the patient and the family. It is generally agreed that the optimal treatment approach is one that combines medication and psychosocial interventions. In

fact, family and patient psychoeducation, which provides information about the nature, origins, and management of psychosis, should begin as early as the initial assessment (Gadelha et al., 2012). Family psychoeducation therapy is an evidence-based practice that is included in the Schizophrenia Patient Outcomes Research Team (PORT) guidelines (Dixon et al., 2010). In addition to improving family members' knowledge of and ability to cope with the symptoms of psychosis, family psychoeducation reduces relapse and hospitalization, in some cases reducing relapse rates by as much as 50% (Lucksted et al., 2012).

Cognitive-behavioral therapy (CBT) for psychotic disorders posits that dysfunctional cognitions can contribute to specific psychotic symptoms (Naeem et al., 2005). CBT for psychosis assumes that the normal cognitive mechanisms are being employed by the patient during periods of nonpsychotic thinking and that these processes can be used to help patients control their symptoms (Naeem et al., 2005). To avoid resistance, psychotic beliefs are not directly challenged; instead, specific symptoms such as hallucinations and delusions are targeted for appraisal of dysfunctional cognitive attributions. Recent reviews of published randomized controlled trials suggest that CBT is effective in reducing the severity of psychotic symptoms (Mueser, Deavers, Penn, & Cassisi, 2013; Rector, Stolar, & Grant, 2011).

The beneficial effects of CBT may be more pronounced when administered to patients earlier in the course of illness. A meta-analysis examining 14 studies including 1,484 patients concluded that CBT produced significant improvements in patient functioning, especially for acute patients, compared with those individuals suffering from chronic schizophrenia (Zimmermann et al., 2005). However, the investigators acknowledge that many moderating factors still need to be evaluated—including the therapeutic alliance, as well as the extent of cognitive deficits during the pretreatment period.

A recent meta-analysis examined the effects of treatment-as-usual (TAU), CBT, and intensive specialized first episode psychosis (FEP) intervention programs that included multidisciplinary teams which provided assertive outreach treatment, evidence-based interventions tailored to patient needs, atypical antipsychotic regimens, manualized CBT strategies, individualized crisis management plans, and family counseling and psychoeducation (Alvarez-Jimenez et al., 2011). The outcome measures were relapse and days of hospitalization. The intense, multimodal intervention provided in the specialized FEP programs was associated with a significantly greater reduction in relapse and days of hospitalization when compared with CBT or TAU alone.

Although research on CBT for preventive intervention has just recently begun, there is also evidence that CBT may be effective in preventing psychosis in CHR youth. A recent meta-analysis of intervention for CHR patients concluded that there was a moderate effect of CBT in reducing symptom severity and transition to psychosis at 12 months (Hutton & Taylor, 2013). To date, this is the most consistent evidence of a preventive intervention effect.

For diagnosed patients, comprehensive programs for supporting the transition back into the community have also been effective in enhancing recovery and reducing relapse. One such program, called Assertive Community Treatment (ACT), was originally developed in the 1970s by researchers in Madison, Wisconsin (Bustillo et al., 2001; Udechuku et al., 2005). ACT is a comprehensive treatment approach for the seriously mentally ill living in the community. Patients are assigned to a multidisciplinary team (nurse, case manager, general physician, and psychiatrist) that has a fixed caseload and a high staff/patient ratio. The team delivers all services to the patient and is available to the patient at all times. Services include home delivery of medication, monitoring of physical and mental health status, in vivo social skills training, and frequent contact with family members. Studies suggest that ACT can reduce time spent in hospital, improve residential stability, and increase patient and family satisfaction (Udechuku et al., 2005).

Social skills training seeks to improve the overall functioning of patients by teaching the skills necessary to improve performance of daily living activities, employment related skills, and interpersonal relationships (Bustillo et al., 2001). Social skills training programs make use of behavioral techniques including modeling, rehearsal, and reinforcement. Recent research indicates that social skills training can improve social competence and treatment compliance (lower social disability and fewer dropouts) compared with structured leisure activities or TAU (Galderisi et al., 2010; Rus-Calafell, Gutiérrez-Maldonado, & Ribas-Sabaté, 2013). However, it remains unclear to what extent this improvement in social competence translates into better functioning in the community. The 2009 PORT guidelines recommend that social skills training be accompanied by strategies to increase real-world use of the skills obtained in therapy (Dixon et al., 2010).

Because the rate of competitive employment for the severely mentally ill is very low, vocational rehabilitation has also been a major focus of many treatment programs. Vocational rehabilitation programs have a positive influence on work-related activities, although they have not yet been shown to have a substantial impact on patients' abilities to obtain employment in the community

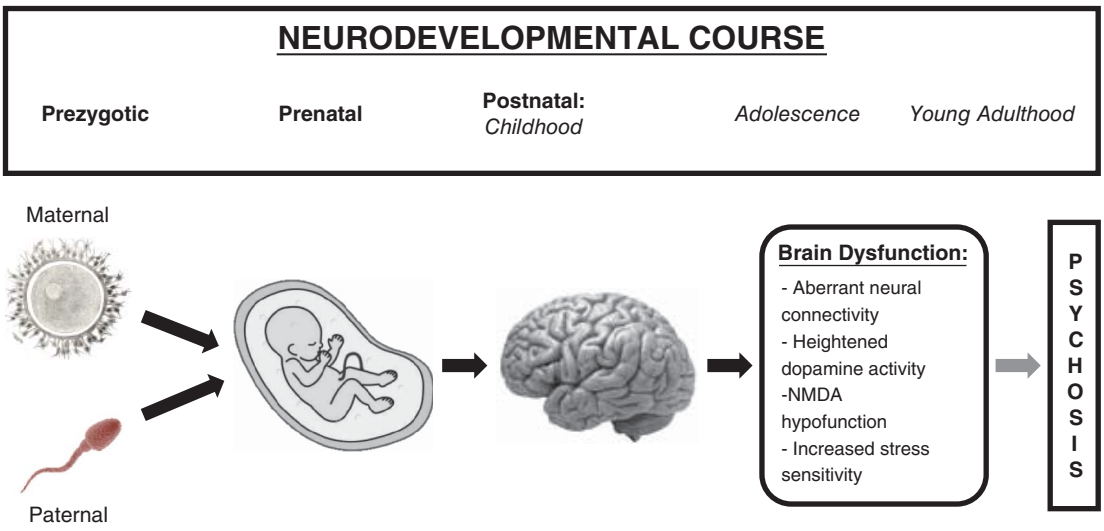
(Lehman et al., 2002). Some evidence suggests that supported employment programs produce better results than traditional vocational rehabilitation programs—as measured by patients' ability to obtain competitive, independent employment. Nonetheless, job retention remains a significant problem, and this prevents young, first-episode patients from establishing self-sufficiency (Bustillo et al., 2001; Lehman et al., 2002).

In summary, a multimodal approach to the treatment of psychotic disorders, combining both medication and psychosocial interventions, appears to be the most effective. Such multimodal approaches are, however, very costly, and few patients receive such treatment. Further, for the majority of patients, the aforementioned treatments do not result in complete remission; residual symptoms remain and derail the individual's acquisition of adult social and financial autonomy. To gain leverage in efforts to reduce the burden of serious mental illness, and ultimately provide preventive interventions, we need to refine our understanding of the neural mechanisms that give rise to psychosis during the critical risk period, adolescence/young adulthood.

Neurodevelopmental Models of Etiology

In the previous sections of this chapter, we have documented the dramatic evolution in our understanding of psychotic disorders; the field has shifted from simple models of disorder-specific causal factors to complex models that include influences at multiple levels of analysis. It is apparent that in both normal and abnormal human development, there is interplay between the developing human brain and the environment, both psychosocial and biological. Further, developmental trajectories originate before birth and involve modulating influences through childhood and adolescence.

Figure 22.1 summarizes the risk factors and processes that have been linked with psychotic disorders and the developmental stages at which they initially impinge to potentially alter neurodevelopment. Both the number of potential influences and the role of the physical and psychosocial environmental increase across the prezygotic, prenatal, and postnatal periods. Given our current understanding of the myriad of factors that influence each stage of human brain development, it is to be expected that



Prezygotic Germline Risk Factors	Prenatal Risk Factors	Postnatal Risk Factors
• Risk Alleles • Mutations • Epigenetics	• Mutations • Epigenetics • Maternal infection and inflammation • Maternal Stress • Pregnancy complications • Nutritional deficiency	• Epigenetic processes • Substance use: Cannabis, Amphetamines • Neuroinflammatory processes • Head injury • Psychological trauma and stress • Aberrant neurodevelopmental processes (e.g., heightened endogenous HPA activity, synaptic pruning, myelination)

Figure 22.1 Risk factors and developmental stages psychosis.

the pathways to psychosis-spectrum disorders are varied and complex. Thus a confluence of interacting factors is assumed to contribute to the neurocircuitry dysfunctions that give rise to various psychiatric syndromes, including psychosis.

In this section, we examine some contemporary models of etiology. Although these models differ in their emphases, they share assumptions about the origins of vulnerability, as well as some of the neurobiological mechanisms that give rise to its expression. To set the stage for this discussion, several points about the issues of etiologic specificity and developmental processes should be reiterated.

As stated earlier, we have not, to date, identified biomarkers that are specific to schizophrenia, or even to psychosis in general. At the level of the measurable behavioral phenotypes that we define as syndromes, there is increasing evidence of nonspecificity in the distal (e.g., genetics, prenatal complications) and proximal (e.g., stress, neuroinflammation) risk/etiologic factors. In fact, many risk/etiological factors cross the diagnostic boundaries among psychotic, mood, and autistic-spectrum disorders. This does not mean that there are no diagnosis-specific, downstream neuropathological processes in psychosis, but rather that they can be triggered by a broad range of nonspecific factors.

Indeed, it is the burgeoning evidence of nonspecificity that prompted the recent introduction of the research domain criteria (RDoC) by the National Institute of Mental Health (NIMH; Cuthbert & Insel, 2013). The RDoC is a research classification system for mental disorders that is based upon dimensions and systems of neurobiology and behavior. It was developed by the NIMH in response to concerns that the *DSM-5*, and other diagnostic taxonomies for mental disorders rely solely on presenting signs and symptoms, do not adequately reflect neurobiological and behavioral systems, and draw diagnostic boundaries that are not empirically supported, thereby impeding research on etiology, neuropathology, and intervention. Thus, RDoC is intended to encourage research on fundamental biobehavioral dimensions that cut across current disorder categories.

In addition to encompassing more nonspecific etiologic factors (e.g., stress, neuroinflammatory pathways), contemporary models are also characterized by a greater recognition of developmental processes. Although the assumption that psychosis involves neurodevelopmental processes arose in the 80s, the initial focus was on prenatal development (Lewis and Murray, 1987), whereas more recent etiologic models have shifted their focus to adolescent development and the prodromal period. And, as mentioned, this shift has corresponded with major advances in our understanding of normative postpubertal neurobiological changes, particularly in brain morphology and function.

A comprehensive review of etiologic models of psychosis is beyond the scope of this chapter. Instead, the ensuing discussion highlights some recent models that attempt to encompass new research findings and to account for the modal trajectory in which prodromal symptoms emerge in adolescence. These models share in common the assumption that vulnerability typically originates in genetic and prenatal/perinatal factors that set the stage for psychosis, but that adolescent neurodevelopmental processes are triggering the expression of vulnerability.

Stress has been implicated in the etiology of psychosis for many decades, but theorizing about the biological mechanisms mediating this effect and triggering psychosis only later entered into the discussion. Walker and colleagues (Walker & Diforio, 1997; Walker et al., 2008) proposed a neural diathesis-stress model that posits a congenital abnormality in striatal DA circuitry that is moderated in its expression by the activation of the HPA axis via both external stressors and endogenous neurodevelopmental processes. This model draws upon extensive evidence that measures of HPA activity are elevated in patients with schizophrenia and affective psychoses. It also links HPA activity with a posited downstream neural mechanism in psychosis, in that glucocorticoid release, via activation of the HPA axis, can augment DA activity in the striatum. In addition, it emphasizes the developmental parallels between the normal maturational increase in HPA activity that begins after the onset of puberty and the developmental course of the prodrome to psychosis (Trotman et al., in press).

Since the proposal of the neural–diathesis–stress model, there has been more extensive research on normative adolescent neurodevelopment showing that it is characterized by critical neurobiological changes and appears to be associated with increased biobehavioral sensitivity to stress (Eiland & Romeo, 2012). Postpubertal changes in both gonadal and adrenal hormones, including glucocorticoids, play an important role in epigenetic processes that trigger these processes. In a recent review of the literature on hormones and risk for psychosis, the authors provide an overview of research findings on the relation of steroid hormones with normative changes in brain structure and function and update the neural-diathesis-stress model to incorporate these new findings (Trotman et al., in press). These normative changes include a decline in gray matter during the course of adolescence and into young

adulthood, and this is assumed to subserve the refinement of neural interconnections. Thus, because neurons in many human brain regions have both surface and intracellular receptors for hormones that mediate genomic and nongenomic processes, adolescent hormonal changes are thought to be pivotal for the reorganization of brain structure and circuits.

Consistent with this view, there is now extensive research documenting the adverse effects of elevated glucocorticoids on brain structure/function in animals (Kim & Haller, 2007), and more recent converging evidence of such a relation in humans. For example, a study using fMRI and EEG with administration of synthetic cortisol revealed rapid changes in the functioning and perfusion of the healthy human brain, presumably via nongenomic mechanisms (Strelzyk et al., 2012). At the structural level, studies of healthy and clinical samples have revealed an inverse association between cortisol levels and regional brain volumes in healthy samples (Knoops et al., 2010; Tessner et al., 2007; Walker et al., 2008) and schizophrenia patients (Mondelli et al., 2010). Prospective research has revealed the same relations; baseline cortisol levels were found to be correlated with gray matter volume changes over the course of treatment in youth with anorexia (Mainz et al., 2012). Further, increases in gray matter were associated with decreases in cortisol when measured simultaneously across time in anorexia patients (Castro-Fornieles et al., 2009). Similarly, in youth with trauma exposure, cortisol levels are negatively correlated with volume in the prefrontal cortex and predict longitudinal declines in hippocampal volume (Carrion & Wong, 2012). Conversely, the reduction of cortisol levels in Cushing's patients is associated with an increase in brain volume and a decrease in psychiatric symptoms (Hook et al., 2007). This suggests that some of the adverse effects of heightened glucocorticoids on brain structure may be reversible.

For individuals who are vulnerable to psychosis, elevated cortisol secretion during the course of adolescence may trigger the expression of risk genes or interfere with epigenetic processes in a manner that leads to aberrant brain development, such as the exaggerated postpubertal decreases in gray matter volume and neuronal connectivity observed in CHR youth. When coupled with increased DA activity, as suggested by previously reviewed findings, this would be expected to result in abnormal function of neural circuits that govern perceptual and thought processes.

In contrast to the previous emphasis on stress biology, some recent perspectives on the neurodevelopmental processes in psychotic disorders have incorporated a greater emphasis on the immune system (Anderson & Maes, 2013; Kinney et al., 2010; Meyer, 2013). As described earlier in this chapter, activation of the HPA axis and activation of immune processes are linked with similar neurochemical and neuroanatomical changes, and their effects are mutually mediated and synergistic (Zunszain et al., 2011). Thus, while glucocorticoids have anti-inflammatory effects at low/moderate levels, it has been demonstrated that exposure to persistent stress or the administration of glucocorticoids can increase the pro-inflammatory response to an immune challenge (Catena-Dell'Osso et al., 2011; Frank et al., 2010). Conversely, activation of the immune response can augment HPA activity (Perez, Bottasso, & Savino, 2009). If persistent, both can be associated with neuroregressive and neurodegenerative processes (Zunszain et al., 2011).

In his recent neurodevelopmental model of psychosis, Meyer (2013) suggests how altered prenatal immune function might set the stage for vulnerability and moderate the course of subsequent development. He first reviews the evidence linking psychosis with prenatal exposure to a range of infections (e.g., viral and bacterial), which gave rise to maternal/fetal inflammatory responses (the prenatal cytokine hypotheses), as well as evidence showing increased proinflammatory responses in schizophrenia. He then offers an account of how prenatal exposure to immune challenge can contribute to early pre- and postnatal alterations in inflammatory response systems, and disrupt subsequent neuronal circuit development. Under normal circumstances, homeostatic processes control inflammatory responses; in the brain, microglia and astrocytes play a pivotal role in modulating inflammatory processes, via the production and regulation of cytokines. But these processes, and the associated neurotropic and neurodegenerative effects of cytokines, vary with developmental stage. For example, Meyer (2013) reviews evidence that exposure to prenatal infection and cytokines is linked with abnormal development of the DA system in animal models, as well as structural brain abnormalities (e.g., ventricular enlargement and reduced cortical volume) in human adults. Yet some effects of prenatal infection on brain development only become apparent in postpubescence, when previously dormant neuroinflammatory abnormalities are activated, possibly resulting in derailment of normal adolescent neuromaturational processes, such as myelination, synaptic pruning, and neuronal remodeling. Meyer emphasizes the role that physical and psychological stressors play in this process, and suggests that stress, glucocorticoid elevations, and release of excitotoxic levels of glutamate by activated microglia may contribute to the exaggerated decrease in gray matter volume and heightened glutamate levels

observed in CHR samples, especially in the transition to psychosis. A very similar model is posited by Anderson and Maes (2013), but with a greater emphasis on oxidative stress pathways.

With a greater focus on adolescent developmental processes, Kinney and colleagues (2010) proposed a model that emphasizes how pro-inflammatory cytokines exacerbate risk for psychosis onset in adolescence/young adulthood due to developmental changes in immune function. In addition to the aforementioned findings, they draw on two lines of evidence: (1) alleles associated with increased risk for schizophrenia also affect the activity of pro-inflammatory cytokines; and (2) an excessive inflammatory response can produce an imbalance of glutamatergic and dopaminergic neurotransmission that leads to psychotic symptoms and a progressive loss of brain tissue that contributes to cognitive deficits. Like Meyer (2013), these authors assumed that prenatal factors can confer a latent vulnerability in the immune system that is relatively dormant until puberty. In particular, they note that prenatal exposure to maternal stress, nutritional deficiency, and infection can lead to thymus gland dysfunction in offspring, which is subsequently heightened during adolescence when the thymus gland normally regresses in volume. The thymus gland is important to the immune system because it produces T-cells which play a central role in adaptive immune function. With atrophy of the thymus in adolescence, latent immune vulnerability is manifested, and individuals become more susceptible to infections or immune diseases that can contribute to the onset of psychosis. Further, Kinney and colleagues (2010) emphasized the deleterious effects of stress and glucocorticoids on immune function, as well as the evidence that neuroinflammation and the pro-inflammatory cytokines (e.g., TNF-α) adversely affect neurogenesis, synapse formation, neuronal connectivity, and the survival of neurons. Related to this model, it is relevant to note that a key feature of 22q11.2 deletion syndrome, which is associated with a 20 to 30 fold increase in risk for psychosis, is early loss of the thymus resulting in reduced T-cells, immune deficiency, and reduced resistance to infection (Bassett & Chow, 2008; Shapiro et al., 2011), It is noteworthy that this genetic cause of thymus dysfunction in humans is also linked with a dramatic increase in risk for psychosis.

Some other neurodevelopmental models have focused greater attention on the brain circuitry or connectivity changes associated with psychosis. For example, it has been proposed that genetic and other factors can lead to early developmental disruptions in intra- and interregional connectivity, and thereby give rise to a psychosis vulnerability that is expressed in late adolescence/early adulthood (Karlsgodt et al., 2008; Uhlhaas & Singer, 2011). These models draw on research findings that psychotic disorders are associated with postmortem evidence of reductions in synapse density and dendritic complexity, as well as findings from *in vivo* MRI studies showing white matter changes indicative of deficient connections among cortical regions. The functional expression of abnormal connectivity, in the form of prodromal symptoms, may arise in adolescence because pre-existing abnormalities interact with the normal adolescent process of synaptic pruning or because the pruning process itself is abnormal. At the level of neurotransmitters, one recent model emphasizes the importance of circuits in the prefrontal cortex that involve glutamatergic and gamma-aminobutyric acid (GABA)-ergic transmission and are characterized by heightened sensitivity to environmental perturbation during adolescent development (Hoftman & Lewis, 2011). Again, these connectivity models incorporate stress systems as one of the mechanisms contributing to circuitry abnormalities.

The previously reviewed etiologic models exemplify the variety of plausible neurodevelopmental processes that might give rise to psychosis. It is possible that each provides an accurate account of the etiologic process for a subgroup of individuals who succumb to psychosis. In fact, it is arguable that the search for etiologic subtypes should be a major focus of future research in the field of psychosis.

FUTURE RESEARCH DIRECTIONS

The now overwhelming evidence that there are diverse and complex risk factors and developmental pathways to psychosis should inform our approach to future research. At the level of the measurable behavioral phenotypes that we define as syndromes, there is not yet evidence of specificity in the distal (e.g., genetics, prenatal complications) or proximal (e.g., stress, neuroinflammation) risk/etiologic factors for various psychotic disorders. In fact, there is growing evidence of multifinality, such that many risk/etiological factors cross the diagnostic boundaries among psychotic, mood, and autistic-spectrum disorders. As reflected in RDoC, the primary goal of contemporary psychiatric research should not be to identify *DSM* disorder-specific causal factors, but rather constellations of factors that, a) are linked with one or more psychiatric syndromes or symptom dimensions, and b) suggest modifiable pathways for intervention.

Before turning to a discussion of promising research approaches, it is relevant to consider some of the challenges that confront clinical research on psychosis. First, it is important to consider that the rate of psychotropic prescriptions has increased dramatically in recent decades, and this is especially true of youth. It is considered best practice to promptly initiate antipsychotic medication to patients who meet criteria for a psychotic disorder (Kreyenbuhl, Buchanan, Dickerson, & Dixon, 2010). For ethical reasons, researchers usually do not manipulate medication status, with the exception of clinical trial protocols which typically involve small samples. Instead, most clinical studies of psychotic disorders are naturalistic studies in which medication status is determined by the participant's treatment provider. Because these medications can have significant effects on brain function and structure, they can obscure the natural course of the illness and complicate cross sectional comparisons between clinical and control groups.

One advantage of research on individuals at-risk for psychosis is that they are less likely than diagnosed patients to be on a psychotropic. Nonetheless, most young people (>60%) who manifest clinical signs of risk for psychosis have a history of receiving one or more psychotropic medications (Cadenhead et al., 2010). Further, the prescription of a psychotropic drug, including antipsychotic or antidepressant medication, is presumably determined by the treatment provider's judgment concerning the patient's symptom severity. Thus, if researchers were to exclude prospective participants who have a history of psychotropic medication, the resultant sample would be nonrepresentative of CHR youth. To deal with this problem, investigators often include medication status as a covariate in statistical analyses. But if the prescription of medication is even partially determined by preexisting behavioral or biological factors, this is not the optimal solution. A clear illustration of the challenges posed by psychotropic medication is in the study of biological and behavioral measures of stress. Antipsychotics and antidepressants can dampen both symptom severity and HPA activity. Thus, CHR participants who are on medication may have experienced a medication-induced dampening of symptoms and HPA activity prior to enrollment in the study. This would, of course, reduce the magnitude of any difference in symptom severity and cortisol levels, as well as other biomarkers, between the CHR and control groups. It would also obscure differences in baseline cortisol in cross sectional comparisons of the medicated and nonmedicated CHR subgroups.

Similar challenges are posed by psychosocial treatments. In addition to higher rates of psychotropic medication, it is not surprising that CHR youth also have a higher rate of lifetime psychological treatment, especially individual therapy. In the first phase of the NAPLS study, about 74% had a lifetime history of psychotherapy and almost half were currently in psychotherapy (Cadenhead et al., 2010). Again, it is reasonable to assume that this treatment is not randomly distributed among participants, but is instead correlated with the severity or longevity of their behavioral symptoms. It is also likely that the psychosocial interventions are successful in reducing symptom severity and enhancing coping in many CHR youth.

The research challenges posed by treatment effects have alerted investigators to the benefits of longitudinal over cross sectional research designs. Longitudinal approaches make it possible to examine within-individual changes in biological and behavioral factors while taking baseline conditions into consideration. It is also assumed that the benefits of longitudinal approaches are enhanced when they are applied to critical developmental periods; in the case of psychosis this is primarily the adolescent period. Of course, nonexperimental, longitudinal research does not eliminate problems with the identification of causal pathways to psychosis. It is plausible, for example, that the biomarkers that have been identified in psychotic and CHR samples (e.g., inflammatory processes, oxidative stress, heightened HPA and DA activity, reduced NMDA function, and brain volumetric abnormalities) are the consequence of a latent neuropathological process, rather than mediators in causal pathways. While nonexperimental research cannot unequivocally distinguish among the many alternatives, there is great potential for longitudinal studies that simultaneously and repeatedly measure behavioral functions and biomarkers as they unfold during critical developmental periods. These approaches will yield data that provide firmer bases for inferring causal processes. By obtaining repeated indices over time, and conducting analyses that detect temporally lagged interrelations among them, there is greater opportunity for detecting relations that reflect causal mechanisms.

Moreover, when combined with controlled intervention trials, longitudinal research designs hold great promise for elucidating causal processes (Cicchetti, 2013). There are, for example, numerous interventions, both psychological and biological, that have the potential to modulate stress and neuroinflammatory pathways. Investigations aimed at examining the effects of such interventions in CHR individuals are now ongoing. Combining intervention trials with longitudinal measurement of biomarkers and behavior will likely yield important information about neural mechanisms as well as optimal intervention strategies.

The burgeoning field of research on the prodrome to psychosis is premised on the assumption that preventive intervention is a feasible goal. Indeed, the fact that psychotic disorders typically arise during adolescence/early adulthood suggests that neurohormonal and neurodevelopmental processes taking place during this period are triggering expression. Indeed, the only other periods in the human life span with a significant increase in risk for psychotic illness onset, namely the postpartum and menopausal periods, are also characterized by significant neurohormonal changes. This suggests the possibility that there are neurobiological processes that can be modulated during these periods to prevent illness onset. Lending further support to the notion that neurohormonal and neurotransmitter modulation holds promise for ameliorating positive psychotic symptoms is the fact that, for most patients, including those on antipsychotic medication, psychosis is episodic with intervening periods of higher functioning after the first episode. Thus, research on the neurodevelopmental precursors of psychosis may also yield insights into the prevention of remission after the clinical onset of the first episode of psychosis.

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CHAPTER 23

Toward a Unifying Perspective on Personality Pathology Across the Life Span

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CONSIDERING PERSONALITY PATHOLOGY IN A DEVELOPMENTAL PSYCHOPATHOLOGY FRAMEWORK

A developmental psychopathology framework clarifies many aspects of the scientific approach (Cicchetti & Toth, 2009), several of which will be discussed here as particularly relevant to the *development* of youth *personality disorders (PDs)*, or *personality pathology*. One important tenet of the developmental psychopathology framework is the need to study normal and abnormal development alongside one another and examine the interaction of factors representing both risk and resiliency. That is, a factor may represent risk (or resiliency) in one context but not another. An increasingly nuanced understanding of contextual features is thus required to elucidate the nature of risk/resiliency and better understand the emergence of psychopathology. This tenet is highly relevant to the broader domain of PDs, as PDs reflect diagnostic constructs which have a rich and expansive literature on their normal counterparts (i.e., normal-range personality). In addition, unlike many other diagnostic constructs, theoretical models and assessment tools for PDs have often drawn on and been integrally linked to models and measures of normal-range personality (e.g., Krueger & Tackett, 2003).

This juxtaposition of normal and abnormal constructs is even more fully realized in a move to better understand PDs in early life (Tackett, Balsis, Oltmanns, & Krueger, 2009). Specifically, previous versions of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) have severely restricted diagnosis of PDs prior to age 18 (which we discuss more later on in the current chapter). Restriction of diagnosis inevitably leads to restricted research and, thus, restricted knowledge of how PD constructs manifest in early life. Research on normal-range child personality and temperament, while lagging behind similar work in adults, can thus be especially useful in working toward a better understanding of PDs in early life. In addition, the use of dimensional trait models in temperament and child personality research are particularly amenable to developmental investigations, as they offer an opportunity to follow a more nuanced conceptualization of stability and change, as well as of risk and resiliency, over the life span (Tackett et al., 2009).

Other features of the developmental psychopathology framework, including the emphasis on simultaneously examining multiple levels of analysis in understanding psychopathology development and the importance of concepts such as equifinality (different starting points result in similar developmental outcomes) and multifinality (the

same starting point results in different developmental outcomes) also hold great relevance for the development of PDs, and will be integrated throughout the chapter as appropriate (Cicchetti & Toth, 2009). We tackled the topic of PD development from a number of perspectives in the current chapter. First, we provide a brief overview of normal-range temperament and personality models in children, which have great relevance for the development of pathological personality across the life span. In this section we also summarize research on the development of normal-range personality across the life span. Next, we move to the conceptualization of PDs in *childhood* and *adolescence* and in later life. First, we review research on the development of PDs in childhood and adolescence and in later life. Then, we tackle conceptualization of PDs in the *DSM* and the resultant developmental implications, as well as measurement issues for PDs in both early and later life. Finally, we discuss four core components of PDs: traits, emotions, interpersonal features, and identity; relevant theory and research are reviewed in each of these domains for early life (childhood and adolescence) and for later life. We then review critical developmental periods for PDs: (1) infancy–toddlerhood; (2) middle childhood–early adolescence; (3) late adolescence–early adulthood; and (4) later life. We conclude the chapter with an overarching summary and future directions.

DEFINING NORMAL PERSONALITY

Normal personality is often defined as an individual's characteristic patterns of behaving, feeling, and thinking, which are relatively stable across time and across situations. Researchers studying adult populations typically label these traits as personality, whereas researchers studying child populations have often labeled them as temperament (Shiner & Caspi, 2003; Tackett, 2006). Historical conceptualizations have suggested that temperament traits are distinct in that they are more biologically influenced and present from early in life (Tackett, 2006), although the lines between these two domains has grown increasingly blurred (De Pauw & Mervielde, 2010; Herzhoff & Tackett, 2012; Rothbart & Ahadi, 1994; Rothbart, Ahadi, & Evans, 2000; Shiner, 1998, 2006; Shiner & Caspi, 2003). Despite this growing consensus that temperament and *personality traits* are more alike than different, important differences remain in their conceptualization which has implications for differences in measurement (Tackett, Kushner, De Fruyt, & Mervielde, 2013).

Two common and widely used models of personality and temperament are the Five-Factor model (FFM; see Goldberg, 1993) and Rothbart's biosocial model of temperament (Rothbart, Ahadi, Hershey, & Fisher, 2001), respectively. The FFM encompasses the following five higher order factors of personality: (1) neuroticism—the tendency to experience negative emotions such as anger, fear, and sadness; (2) extraversion—the tendency to experience positive emotions, be active, and social; (3) agreeableness—the tendency to experience affiliation and empathy; (4) conscientiousness—the tendency to experience achievement motivation and be orderly; and (5) openness-to-experience—the tendency to value new experiences, be intellectually curious, and imaginative. In contrast, Rothbart's model encompasses three higher order factors of temperament: (1) negative affectivity (akin to neuroticism); (2) positive emotionality/surgency (akin to extraversion); and (3) effortful control (akin to conscientiousness).

Despite their difference in number of factors, three- and five-factor models of personality have been hierarchically linked in studies with both adults (Markon, Krueger, & Watson, 2005; Tackett, Quilty, Sellbom, Rector, & Bagby, 2008) and children (Tackett, Krueger, Iacono, McGue, 2008). At the highest level, 2-factor models of personality typically include negative affectivity/neuroticism and extraversion/surgency traits (e.g., Digman, 1997; Gray, 1987). Three-factor models, as previously described, typically include a third trait indexing constraint or self-regulatory capacities, which typically breaks off from neuroticism at level 2 (Tellegen, 1985). At level 4, this broad constraint trait splits into intrapersonal constraint (i.e., conscientiousness) and interpersonal constraint (i.e., agreeableness), a distinction in self-regulatory capacities that only begins to appear in temperament measures in adolescence (Ellis & Rothbart, 2001). Finally, at level 5, openness splits off from extraversion, signifying a distinction between nonsocial and social approach-motivated behaviors that are not explicitly found in major temperament models (but see Herzhoff & Tackett, 2012). Therefore, although the temperament and personality literatures have historically developed separately from one another—and important differences remain (Tackett, Kushner, et al., 2013), hierarchical approaches suggest that they may not reflect meaningful developmental differences, but rather, differences in the level of the hierarchy focused on for a particular framework.

At lower levels of the personality hierarchy, more narrowly defined traits—or facets—reside. For example, fear/anxiety is a facet of neuroticism/negative affectivity as measured by both a common personality measure, the revised NEO Personality Inventory (Costa & McCrae, 1992), and a common temperament measure, the Children's

Behavior Questionnaire (Rothbart et al., 2001). Although such lower order traits have been found to have great predictive value for psychopathology (e.g., Reynolds & Clark, 2001), the field of temperament/child personality research is far from a consensus structure of lower order traits across development (Tackett, 2006). More empirical studies are needed to explore both the structural and developmental relationships between temperament and personality at different levels of the hierarchy (Shiner & Caspi, 2003), and as researchers move toward greater agreement regarding the higher order structure of personality in childhood, it is likely that future efforts will begin to demonstrate similar progress in delineating the universe of childhood personality facets.

Although the trait approach dominates empirical research on personality across the life span, other personality constructs also show great relevance to development and psychopathological outcomes. For example, Shiner (2009) has discussed the relevance of McAdams and Pals (2006) multi-level personality framework for the development of PD in youth. Specifically, McAdams and Pals differentiate traits (level 1) from characteristic adaptations (level 2) and personal narratives (level 3). Constructs at all levels are relevant for the development of PDs, not just traits (Shiner, 2009; Shiner & Tackett, 2014). For example, attachment patterns and emotion regulation would fall under level 2 of the McAdams and Pals model as they are not well captured by current personality trait frameworks, yet show enormous import for the development of PDs in youth (Shiner, 2009; Shiner & Tackett, 2014). Similarly, identity development is a key component of personal narratives and is similarly fundamental to an understanding of PD development. Thus, it is important to think broadly when considering the normative personality context within which PD development takes place.

Life Span Development of Normal Personality

Although personality is defined as a relatively stable tendency to behave, think, and feel across situations, studies on the life span development of normal personality reflect robust evidence for both stability and change (Fraley & Roberts, 2005). Long-term longitudinal studies have found that personality/temperament assessed as early as age 3 predicts personality in adulthood as much as 40 years later, suggesting that personality is relatively stable across development (Caspi, 2000; Caspi et al., 2003; Caspi & Silva, 1995; Nave, Sherman, Funder, Hampson, & Goldberg, 2010). This continuity seems to be largely due to genetic and nonshared environmental factors (De Fruyt et al., 2006) and seems to be similar in magnitude across community and clinical samples (De Bolle et al., 2009). Personality psychologists further differentiate between multiple types of stability, or continuity. For example, mean-level stability reflects continuity in absolute levels of personality traits across time, whereas differential continuity (or rank-order stability) refers to continuity in an individual's relative level, or ranking, on a trait relative to a broader population (De Fruyt et al., 2006). Both types of continuity, as well as additional aspects of personality stability, have been studied in populations ranging from childhood to older age. We broadly summarize findings on mean-level and rank-order stability, consider investigations on continuity for personality types which have received substantial attention in childhood and adolescence, and briefly acknowledge additional considerations including measurement issues and individual variability.

Mean-level Stability

The best accounting for life span mean-level stability in personality traits comes from a seminal meta-analysis (Roberts, Walton, & Viechtbauer, 2006). This study found that mean-levels of social dominance, conscientiousness, and emotional stability increased across the life span—especially between ages 20 and 40 years, that social vitality and openness increased in adolescence and then decreased in old age, and that agreeableness increased only in old age (Roberts et al., 2006). Examinations of mean-level stability, in both reviews and independent empirical investigations, have often noted that changes in adult personality tend to happen in the direction of greater maturity, such that most individuals are most likely to increase in their dominance and self-confidence and decrease in their anger and alienation, with more mature individuals changing less than less-mature individuals (Roberts, Caspi, & Moffitt, 2001). More recent investigations of mean-level stability have dedicated focused attention to understanding mean-level changes in childhood and early-mid adolescence. Findings from these studies have not always supported evidence for mean-level stability of personality traits in childhood and adolescence (De Fruyt et al., 2006), and have even hinted that personality traits may progress from more to less maturity between childhood and adolescence, with increased maturity of personality primarily reflecting the later stages of adolescent development and adulthood (Soto, John, Gosling, & Potter, 2011). Such work has been very limited to date in early life, representing an important area for future research.

Rank-order Stability

Roberts and DelVecchio (2000) contributed another seminal study on life span personality development: a meta-analysis on the rank-order stability of personality. These findings suggested that rank-order stability of normal personality traits increased across the life span from childhood to age 50 years, stabilizing until age 70 years (Roberts & DeVecchio, 2000). Importantly, these findings countered previous suggestions that personality did not stabilize until adulthood, such that even in early childhood, evidence for substantial continuity was found as well. In terms of differences in stability across traits, results suggest that stability tends to be highest for extraversion and lowest for neuroticism (Roberts & DelVecchio, 2000). This is true for samples in childhood and adolescence (De Fruyt, et al., 2006; Tackett, et al., 2008) as well as into adulthood (Hampson & Goldberg, 2006).

Personality Types

Other investigations of personality stability have focused on personality types or profiles (e.g., overcontrolled, undercontrolled, and resilient types), rather than traits. Stability of personality types appears to be moderate in adolescence (Akse, Hale, Engels, Raaijmakers, Meeus, 2007; Meeus, Van de Schoot, Klimstra, & Branje, 2011) and to increase with age (Klimstra, Hale, Raaijmakers, Branje, & Meeus, 2009). Of the adolescents who change profiles, most change only once (Meeus et al., 2011) and of the changes that happen, most happen toward greater maturity, e.g., either from undercontrolled to resilient or overcontrolled to resilient (Meeus et al., 2011), or from undercontrolled to overcontrolled (Akse et al., 2007). This change toward greater maturity results in a decreasing percentage of over- and undercontrollers and an increasing percentage of the resilient types from early to late adolescence, consistent with the maturity trends previously noted for personality traits. Interestingly, whether one's profile is similar to other individuals' profiles in any given developmental period (within-time normativeness) has been found to be more predictive of adjustment than whether one's profile at one point in time is similar to one's profile at another point in time (distinctive stability; Klimstra et al., 2009).

Additional Considerations

Studies of normative personality development have been sparse, particularly at earlier ages, and more work in this area is needed. In addition, existing work has pointed toward a number of considerations for future studies in this area. Measurement considerations remain an important concern for understanding and interpreting longitudinal studies of personality development. For example, meta-analyses typically find that the longer the time between assessments, the greater the change in personality, i.e., the lower the rank-order consistency and the greater the mean-level change (Roberts & DelVecchio, 2000; Roberts et al., 2006). Furthermore, meta-analyses (Roberts & DelVecchio, 2000; Roberts et al., 2006) and other studies (e.g., Hampson & Goldberg, 2006) have suggested that the younger the sample, the greater the change in personality, e.g., temperament measures, which are used more frequently in younger samples, typically show lower rank-order consistency and younger samples also tend to show greater mean-level change. These findings are in contrast to studies employing measures of child personality (De Fruyt et al., 2006), and highlight the need to better understand the extent to which measurement problems in the area of child personality confound perceptions of instability (e.g., Tackett et al., 2012). In addition, cross sectional studies offer some insight into potential mean-level changes in childhood and adolescence, but are clearly less desirable than longitudinal studies to pick up on true developmental changes (Klimstra et al., 2009).

Another important measurement consideration is moving beyond broad personality trait domains to investigate facet-level traits (De Fruyt et al., 2006; Soto et al., 2011; Soto & John, 2012). For example, one study found that although the higher order conscientiousness trait increased across age, only its lower order facet Industriousness showed a similar pattern, suggesting that studies on the development of personality across the life span should take into account possibly divergent facet-level changes that might be masked by domain-level changes (Soto et al., 2011; Soto & John, 2012). Soto and John (2012) further found that changes in one domain or facet were not related to changes in another domain or facet, suggesting that mechanisms for personality change operate narrowly on one trait rather than broadly on domains. Such work, of course, also requires more careful attention to delineation and assessment of personality facets in childhood, an area which is severely underdeveloped. Studies relying on personality facets established in adults provide an important contribution to this area, but work focused specifically on personality facets developed for younger populations will be necessary.

A final consideration to note is the issue of individual variability. Despite increasing consistency of personality across development, individual differences in the trajectories of personality also exist, such that some individuals stay relatively stable in their personality, whereas others

decrease or increase in their trait levels over time (e.g., De Fruyt et al., 2006; Mroczek & Spiro, 2003; Vaidya et al., 2008). For example, a study on a large sample of men between the ages of 43 and 91 years found that individual differences in trajectories for extraversion and neuroticism existed across a span of 12 years (Mroczek & Spiro, 2003). Specifically, this study found that although extraversion changed linearly whereas neuroticism declined quadratically *on average*, individual differences in the level and rate of change also emerged. These individual differences were predicted by birth cohort and age-related life events such as marriage, death of a spouse, and memory problems. Age-related life changes with regard to social roles and physical health have also been found to predict personality change in middle-aged women (Helson & Soto, 2005), suggesting that normative changes in personality (e.g., changes toward more maturity) that have been found across different studies (e.g., Akse et al., 2007; Meeus et al., 2011; Roberts et al., 2001; Soto et al., 2011) might be due to normative changes in social roles across life.

In sum, research examining personality continuity has demonstrated evidence for both stability and change across the life span. Previous notions of primary instability in childhood personality, as well as rigid stability from early adulthood onward, are clearly outdated. Modern conceptualizations of normal-range personality development allow room for both stability and change across the life span, and highlight increasingly sophisticated and nuanced approaches to thinking about personality continuity over time.

DEFINING PD ACROSS THE LIFE SPAN

PDs are disturbed characterological patterns of thinking, feeling, behaving, and relating to others. In a broad sense, PDs or pathology defines those instances when normal personality (individual patterns of thoughts, feelings, and behavior) becomes rigid and inflexible, and results in impairment for the individual and others around them. A number of core constructs are thought to define personality pathology, including rigidity (lack of adaptability of one's characteristics to the environment or circumstance), lack of insight and self-awareness, problems in the area of self (e.g., identity), and problems in the area of relationships. In the following section, we review longitudinal investigations of *DSM*-defined PDs, a *DSM*-based discussion of PDs in later life, a specific discussion of the *DSM* approach to PDs in *DSM-IV-TR* (APA, 2000) and *DSM-5* (*APA,* 2013) and measurement issues for PDs in early and later life. Following that, rather than reviewing developmental issues within the existing *DSM* taxonomy (particularly given the lack of validity for the current categorical classification approach and its lack of developmental sensitivity), we discuss developmental issues in both early and later life for core components of personality pathology that undergird PD diagnoses and represent cross-cutting areas of importance across multiple PD categories. Those core components we discuss are traits, emotions, relationships, and identity.

Historical Context: Longitudinal Studies of PDs

Historically, longitudinal studies of PDs have been limited to adult samples; however, more recently, studies have been expanded to include youth samples as well. Similar to longitudinal studies of normal personality, longitudinal studies of PDs have found that abnormal personality is also moderately to strongly stable from six years of age over a time interval as long as 20 years (e.g., Asarnow, 2005; Bornovalova, Hicks, Iacono, & McGue, 2009; Bornovalova, Hicks, Iacono, & McGue, 2012; Chanen, et al., 2004; Cohen, Crawford, Johnson, & Kasen, 2005; Crick, Murray-Close, & Woods, 2005; De Clercq, Van Leeuwen, Van den Noortgate, De Bolle, De Fruyt, 2009; Grilo, Becker, Edell, & McGlashan, 2001; Johnson, et al., 2000; Lenzenweger, 1999; Lynam, et al., 2009; Skodol, et al., 2005; Stepp, Pilkonis, Hipwell, Loeber, & Stouthamer-Loeber, 2010; Winograd, Cohen, & Chen, 2008). Also similar to normal personality, this continuity seems to be largely due to genetic and nonshared environmental factors, at least in the case of borderline PD (Bornovalova et al., 2009). We broadly summarize findings on mean-level and rank-order stability of PD and briefly discuss some potential moderators of PD continuity.

Mean-Level Stability

Across several studies, mean levels of most PDs have been found to decrease across the life span in both those individuals who score above a diagnostic threshold as well as those who score below a diagnostic threshold (Gutiérrez et al., 2012; Lenzenweger, 1999; Paris, 2002, 2003; Paris, Brown, Nowlis, 1987; Sanislow et al., 2009; Shea et al., 2002; Skodol et al., 2005). Exceptions to this downward trend seem to be histrionic and obsessive-compulsive traits—which have been found to stay the same, as well as schizoid traits—which have been found to increase across the life span (Gutiérrez et al., 2012). Developmental changes are also seen across childhood and adolescence,

as PD symptoms peak during early adolescence (Bernstein et al., 1993; Cohen, Crawford et al., 2005; Crawford, Cohen, Johnson, Sneed, & Brook, 2004; Johnson et al., 2000) or immediately preceding puberty in the case of borderline PD symptoms (Crick et al., 2005).

Several factors have been identified as moderators of this mean-level continuity of PDs. For example, although a decrease in mean-levels is evident both in community (e.g., Bornovalova et al., 2009, 2012; Crick et al., 2005; De Clercq, Van Leeuwen et al., 2009) and in inpatient samples (Grilo et al., 2001), mean-levels have been found to decrease more sharply for individuals who show lower initial mean-levels than for those who show higher initial mean-levels (Crawford, Cohen, Johnson, Kasen, First, Gordon, & Brook, 2005; De Clercq, Van Leeuwen et al., 2009). This differential change in trait levels therefore creates an increasing gap between the groups with clinically elevated scores and those with relatively low scores. Another moderator of at least borderline PD continuity is gender. Specifically, contrary to Crick et al.'s (2005) hypothesis that girls' borderline PD traits would increase more greatly than would boys' from 4th to 6th grade, girls' traits marginally decreased whereas boys' did not change. A similar moderating effect of gender was not found later in development (15–18-years; Chanen et al., 2004), however.

Trajectories of abnormal personality have also been found to show substantial individual differences in the level and rate of change of severity (Lenzenweger, Johnson, & Willett, 2004). For example, Lenzenweger and colleagues (2004) found the level of severity to be conditional on group membership (i.e., possibly having a PD versus not having a PD) and sex. Specifically, individuals with a possible PD and males showed elevated scores on 8 of the 15 assessed PDs except for histrionic and dependent PDs. Rate of change of severity was found to be conditional only on an individual's possibility of a PD, with those individuals that possibly had a PD showing a greater decline in severity. Furthermore, although borderline PD traits have been found to generally decrease with age (e.g., Johnson et al., 2000), individual differences in psychosocial histories, such as a history of sexual abuse, trauma, poor parenting, stressful life events as well as parental factors such as low socio-economic status and low IQ affect the trajectory of personality pathology. For example, leaving a stressful relationship has been found to coincide with a decrease in borderline personality symptoms (Gunderson et al., 2003) whereas early maternal separation has been found to predict both an increase in borderline personality symptoms as well as a decrease in the reduction of symptoms over time (Crawford, Cohen, Chen, Anglin, & Ehrensaft, 2009).

Whether and how changes in normal personality or temperament affect changes in abnormal personality is unclear, particularly in early life. For example, Warner and colleagues (2004) found that changes in normal personality affected subsequent changes in PDs, whereas the reverse was not true in an adult sample. Lenzenweger and Willett (2009), on the other hand, found that changes in temperament did not affect changes in schizoid PD, in a sample of college students. Little is also known about the reciprocal effects of Axis I and Axis II disorders, even in adulthood. Specifically, the reciprocal effects of Axis I and Axis II disorders may operate in the direction of improvement in Axis II symptoms preceding improvement in Axis I symptoms, at least in the case of borderline PD and major depressive disorder in a sample of adults (Gunderson et al., 2004); however, further studies examining different disorders in different samples are lacking.

Rank-Order Stability

Despite the historical reluctance to diagnose PDs, before adulthood, the stability of abnormal personality in youth is comparable to that in adults (De Clercq, Van Leeuwen, et al., 2009; Grilo & McGlashan, 2005; Johnson et al., 2000). Specifically, even though PD diagnoses in adults have been found to be more stable than diagnoses of Axis I disorders such as Major Depressive Disorder, PD diagnoses do not seem to be as stable as the *DSM*'s description of PDs suggests (Cohen, Crawford, et al., 2005; Grilo et al., 2004; Grilo & McGlashan, 2005; Johnson, Bromley, Bornstein, & Sneed, 2006; Shea et al., 2002; Skodol et al., 2005; Zanarini, Frankenburg, Hennen, Reich, & Silk, 2005). These findings counter suggestions that personality is too unstable before adulthood for a meaningful diagnosis of PD as well as the idea that a diagnosis of PD is set for life and not likely to change.

Several factors have been identified as moderators of the rank-order continuity of personality pathology. For example, in youth, parent-reports of borderline personality traits (Stepp et al., 2010) have been found to show greater stability than have self- (Bornovalova et al., 2009, 2012; Chanen et al., 2004; Crick et al., 2005; Grilo et al., 2001) or teacher reports (e.g., Stepp et al., 2010). Furthermore, stability for parent reports has also been found to show a linear increasing trend whereas teacher reports show a curvilinear trend with a peak between 8 and 11 years (Stepp et al., 2010). Further moderating the effect of reporters

on the stability of abnormal personality are the pathological traits reported on. For example, teacher reports of internalizing aspects of PDs, such as the depressive aspects of BPD, have been found to be less stable than teacher reports of externalizing aspects of PDs, such as hyperactivity aspects of BPD (Stepp et al., 2010). Self-reports of borderline personality traits have not been found to show such differential stability, rather, both internalizing (e.g., boredom and emptiness) and externalizing (e.g., anger) aspects of borderline PD appear to be stable (Garnet, Levy, Mattanah, Edell, McGlashan., 1994; McGlashan et al., 2005; Zanarini et al., 2005), whereas more severely disturbed aspects such as self-harm and suicidality have been found to be the least stable aspects (McGlashan et al., 2005; Meijer, Goedhart, Treffers, 1998; Zanarini et al., 2005).

Given that differential stability is dependent on the personality aspects being studied, Skodol et al. (2005) suggested that PDs could be best conceptualized as made up of two factors: (1) relatively stable abnormal personality traits and (2) maladaptive behaviors aimed to cope with these abnormal traits (e.g., self-injury to cope with emotional tension). Further supporting this conceptualization is the finding that different PDs become more correlated with one another over time, suggesting that an underlying general personality pathology factor might be at play (Sanislow et al., 2009). Such a conceptualization of PDs might also explain the moderating effect of sample composition on PD stability. For example, borderline personality traits are more stable in community (Bornovalova et al., 2009, 2012; Crick et al., 2005; Stepp et al., 2010) and outpatient (Chanen et al., 2004) than in inpatient samples (Grilo et al., 2001; Meijer et al., 1998; Zanarini et al., 2005) potentially because inpatients receive more intense treatment targeted at the most severe and least stable aspects of personality psychopathology (Grilo et al., 2001). This intervention target might also explain the fact that the diagnostic stability of PDs is comparably lower than are mean-level and rank-order stability of PD symptoms and traits (e.g., Chanen et al., 2004; Black, Baumgard, & Bell, 1995; Lofgren, Bemporad, King, & Lindem, 1991; Mattanah, Becker, Levy, Edell, & McGlashan, 1995; Meijer et al. 1998; Skodol et al., 2005; Skodol, 2008).

In sum, longitudinal studies of PDs have come to some similar conclusions as longitudinal studies of normal personality. Specifically, research has demonstrated evidence for both stability and change in abnormal as well as normal personality across the life span. Future studies are still needed to examine the full range of moderators as well as mediators of such stability and change. In addition, most of this work has been with adults, and that with children and adolescents has often relied on adult-based conceptualizations of PDs. More developmentally sensitive studies should investigate empirically based personality pathology constructs in youth and their developmental trajectories over time. Furthermore, there is still a lack of longitudinal studies covering the extreme ends of the life span that might shed light on important developmental changes during those early and late years that can give rise to changes in personality pathology. Next, we discuss the relevance and importance of examining PDs in later life, an understudied area of research.

PDs in Later Life

Do PDs intensify, remain stable, or burn out with age? At first glance, empirical evidence generally suggests the latter, as a few longitudinal studies of varying samples and time lengths have indicated that PDs decrease over time (i.e., Grilo et al., 2004; Johnson et al., 2000; Lenzenweger et al., 2004). Grilo et al. (2004), for example, found that in a clinical sample of mixed-aged adults, PDs remitted for many individuals and there was a significant decrease in the mean number of criteria met in all four analyzed PDs over a two-year period (p. 773). Johnson et al. (2000) found that in a community sample of young adults, PD traits declined by 28% over an approximately 10-year period. And Lenzenweger et al. (2004) found that in a nonclinical sample of college-aged adults, PDs decreased at a rate of about 1.4 diagnostic criteria per year. In sum, the results from select longitudinal studies of PD suggest that PD traits often decrease over time in adults.

Similarly, the results from many cross sectional studies have indicated that PDs are frequently found to be less prevalent in older adults than younger adults (e.g., Casey & Schrodt, 1989; Cohen et al., 1994; Fogel & Westlake, 1990; Gutiérrez et al., 2012; Samuels et al., 2002; Zimmerman & Coryell, 1989), again suggesting that PDs decline with age. In each of these studies, either PD diagnoses or traits were found to be less frequent or less severe in older adults than a comparison group of relatively younger adults. This finding was most pronounced among the externalizing Cluster B disorders (e.g., Cohen et al., 1994; Ferro, Klein, Schwartz, Kasch, & Leader, 1998; Gutiérrez et al., 2012; Samuels et al., 2002; Segal, Hook, & Coolidge, 2001). Alternate explanations for these cross sectional findings are that the PD diagnostic criteria do not function as intended within an older adult sample (see Mroczek, Hurt,

& Berman, 1999) or are perhaps latent during later adulthood. These are intriguing possibilities that we'll return to later in this chapter. The lower prevalence rates in older adults could also be attributable to the fact that PDs are going undetected, not being adequately captured by the diagnostic criteria, or remaining latent due to the changing contexts of later life.

There is no doubt that PDs are problematic when they exist at any point in a person's life (Segal, Zweig, & Molinari, 2012). They frustrate co-workers, disrupt important relationships, and play key roles in the development of many Axis I disorders (Segal, Coolidge, & Rosowsky, 2006). Our understanding of their implications, however, has been largely limited to their examination in early adulthood. How do PDs rear their heads in later life? What are the late life consequences of having a PD? What are the effects of PDs on individuals, their families, and the healthcare system (see Segal, Hersen, Van Hasselt, Silberman, & Roth, 1996)? Currently, we cannot answer these questions definitively because PDs have not been studied extensively in later life (Agronin & Maletta, 2000). But considering the nature of PDs and how they affect younger adults, one would hypothesize that PDs should have very dire consequences in later life. After all, PDs are long, enduring styles of interacting with others and viewing oneself that lead to key social dysfunctions (APA, 2000).

There is some preliminary data and anecdotal evidence suggesting that PDs may cause severe dysfunction in late life. Consider the Cluster A PDs, such as paranoid PD. One can imagine a young man with a certain amount of paranoia. This young man may not be functionally impaired because he has a healthy body and can engage in some amount of self-protection in public if needed. But consider this same man at a much older age. As an older man, he may be relatively frail and this might lead his paranoia to become dysfunctional—he may find himself trapped in his home, afraid to go out now that he can no longer defend himself against an imagined threat. So it would be in late life that the PD might cross some threshold of dysfunction for the first time in a person's life (see Balsis, Gleason, Woods, & Oltmanns for a discussion of this case example).

Cluster B disorders, such as narcissistic PD, can also lead to increased dysfunction in later life (see Rosowsky & Smyer, 1999 or Siegel & Small, 1986, for relevant case studies). In one case study, an older narcissistic woman continued to experience interpersonal problems that left her vulnerable in later life (Balsis, Eaton, Cooper, & Oltmanns, 2010). She reported an overturn in her social network not seen in regular *aging*. She had difficulty maintaining relationships and found herself facing the challenges of later life with no close family and many broken relationships in the past. As physical illness set in, even the simple tasks of recovering from an illness was somewhat difficult for her because she had no one to rely on for help.

Cluster C disorders, such as obsessive-compulsive PDs, can reveal similar difficulties in late life (see Segal, et al., 2006, pp. 124–136). Consider a woman with obsessive-compulsive PD who has a high need for control. When this woman with obsessive-compulsive PD enters late life, she may face health changes that are largely out of her control. In an effort to gain a sense of control, the older woman with obsessive-compulsive PD may begin to demonstrate marked dysfunctional behaviors and experience relationship problems. For example, she may squander money and time on excessive physician appointments and take out additional but unnecessary insurance policies. She may also experience more strained relationships with adult children. Her previously acceptable need to control her own children's behaviors, for example, may become dysfunctional after those children have grown up and become independent. These relationships may become particularly strained as the older woman's need for control becomes more inappropriate in late life.

People with avoidant PD (another Cluster C PD, Segal et al., 2006, pp. 104–117), may also experience increased dysfunction in late life. Unlike those with obsessive-compulsive PD, those with avoidant PD may be unlikely to visit the physician even when they should, due to fear or anxiety. Imagine a man with avoidant PD. As a young man, his avoidant PD may not lead to significant health problems or dysfunction. The decision not to go to the doctor might not have had major consequences because, as a young man, he was probably fairly healthy. But, as an older adult with potentially more health needs, the avoidant PD may become dysfunctional for the first time in this man's life. In essence, age becomes the proverbial straw that breaks the camel's back. For this man, his health issues were growing quietly in early life, and it wasn't until later life that those issues became clinically significant. As these anecdotes and case studies illustrate, personality pathology can have unique pathways to dysfunction in later life.

In addition to the anecdotal evidence and case study evidence that PDs cause dysfunction in later life, there is also relevant research demonstrating that poor social relationships are associated with functional impairment, mortality, and disease (Morack, Ram, Fauth, & Gerstorf,

2013; Rosland, Heisler, & Piette, 2012; Tomaka, Thompson, & Palacios, 2006). By definition, people with PDs have poor social relationships, so it is possible that the presence of a PD is a major mediating factor in the link between poor social relationships and disease and between poor social relationships and mortality. For example, a systematic review of dozens of studies revealed that those with relatively poor support had worse disease-related outcomes, including increased mortality (Rosland et al. 2012). It is quite possible that many of the older adults with poor social support across these studies had significant personality pathology and, thus, clear difficulty cultivating and maintaining a strong social support network. These data and other data from the social support literature offer promising leads for PD researchers interested in connecting PDs to some of the most important health outcomes.

In addition to examining disease and mortality as outcomes, we also can examine how PDs contribute to societal burden (cost in terms of money and other resources). We know that older adults are much more likely to have diseases than are younger adults. And we know that people with PDs are more likely to have diseases and to cost the system more than their peers (Gish et al., 2001; Spiessl, Hubner-Liebermann, Binder, & Cording, 2002; Whiteman, Deary, & Fowkes, 2000). Because older adults are the largest users of the healthcare system and represent much of the cost, older adults with PDs likely cost the system disproportionately more. Supporting evidence for the hypothesis that older adults with PDs place an increased burden on society comes from clinical accounts of older adults attempting to use the health care system (see Rosowsky & Smyer, 1999). Indeed, the 'difficult patient' as Rosowsky and Smyer call them, very well may be the patient with a PD, placing unjustifiable demands on staff members that they can't meet, and responding in disruptive ways to staff and other patients. In sum, these patients tend to wreak havoc on the staff and sometimes on the other patients, require special attention, more time, and can disrupt functioning of even a well-run medical unit.

The discussion thus far suggests that PDs can lead to significant problems in later life. Yet, there is little research directly examining the effect of PDs on late life outcomes. One major study is beginning to comprehensively examine the effect of PDs in later life. The St. Louis Personality and Aging Network (SPAN) study (see Oltmanns, et al., 2014) is one such study that may yield important insights into how PDs in late life affect important psychological and health outcomes. The SPAN study is a prospective, longitudinal study designed to examine personality stability and change over time, as well as the impact of personality pathology on later life outcomes. The main goals of the project are to examine the connections between PDs, health, and social adjustment in a representative, community-based sample of 1,600 people between the ages at intake of 55 and 64. This sample is particularly interesting because the participants in the sample are at a critical age—an age when many people begin to meet the challenges of later life. Results from the SPAN study are promising and are revealing ways PDs and PD traits influence older adults' ability to adapt successfully to important life transitions. The study is also revealing ways that PD traits give rise to certain health consequences. For example, forthcoming results indicate that PDs are associated with serious health problems, diseases such as diabetes and heart disease, and life stressors. The results that are beginning to emerge from the SPAN study are ground-breaking and some of the first to demonstrate a link between PDs and late life health outcomes. But, several questions remain. For example, research will need to examine *how* PDs lead to poor health outcomes, which poor health outcomes, how much PDs cost society, how they affect families, and what can be done to treat them.

Clearly, it will be important to study PDs in late life to answer these questions. But there are significant challenges to studying PDs in late life. First, fundamental measurement issues will need to be addressed. These are measurement issues that plague all PD research, but that are particularly marked when researching PDs in late life (see Zweig, 2008). We turn next to the *DSM* classification of PDs, before discussing specific measurement limitations in both early and later life populations.

The *DSM* Diagnostic Approach

A recent version of the *Diagnostic and Statistical Manual of Mental Disorders*, or *DSM-IV-TR* (APA, 2000) described PDs within a categorical system differentiating 10 individual PDs. This classification system for the PDs has suffered much criticism, including concerns regarding excessive comorbidity both within Axis II and across Axis I and II diagnoses, symptom overlap across disorders, a clustering scheme that has not been empirically supported, and within-category diagnostic heterogeneity (e.g., Clark, 2007; Shiner, 2009; Tackett et al., 2009). The general consensus in the field regarding many of these concerns led to a number of innovative proposals for the PD section in preparation for *DSM-5*. For example, members of the work group discussed possible changes

to the *DSM-5* PD section that might have included the primary use of a dimensional PD trait taxonomy for characterizing and classifying individuals (e.g., Hopwood, Thomas, Markon, Wright, & Krueger, 2012) or the use of narrative-based prototypes for capturing existing PD diagnostic categories (e.g., Skodol et al., 2011). These and other provocative and innovative suggestions resulted in great excitement and controversy in the years leading up to the publication of *DSM-5* (Widiger, 2013). Despite the resulting controversy, it came as a great surprise to most of the field to learn that *no* changes would be made to the PD diagnostic criteria between *DSM-IV-TR* and *DSM-5*, 13 years later (Krueger, 2013; Widiger, 2013).

Specifically, an executive decision resulted in rejection of the work group's various suggestions for change and improvement, such that the *DSM-IV-TR* PD categories and criteria were ultimately decided to be reproduced in their entirety in *DSM-5*, and some of the work group's proposals were also included in Section III (areas suggested for future research). Thus, we can anticipate many of the concerns that have plagued the field for decades now to remain, without a clear, practical solution in sight. These consequences are particularly impactful for the area of early PD emergence and development, as previous versions of the *DSM* have played a major role in limiting the capacity for empirical and clinical attention to early life PDs (Shiner, 2009). Furthermore, a dimensional PD model holds much greater promise for a life span developmental perspective on PDs as well as enhanced juxtaposition of normal and abnormal personality development according to a developmental psychopathology perspective (Tackett et al., 2009).

Thus, the review of literature in the current chapter retains the organizational system published in *DSM-IV-TR* and reprinted verbatim in *DSM-5*. Ten PDs are organized into three clusters: Cluster A, Cluster B, and Cluster C. Cluster A disorders include schizoid, schizotypal, and paranoid PDs. Cluster B disorders include borderline, antisocial, narcissistic, and histrionic PDs. Cluster C disorders include avoidant, obsessive-compulsive, and dependent PDs. No specific provisions are made for PDs at younger ages, although diagnoses prior to age 18 are discouraged (and practically, have been treated as largely restricted). We incorporate this existing scheme into the current chapter out of necessity, but instead of reviewing each disorder (or cluster) individually, we instead tackle those core underlying components that are central and cross-cutting to all PDs: traits, emotions, interpersonal relationships, and identity. First, however, we review measurement issues in assessing personality pathology in early and later life.

Measurement Issues in Childhood and Adolescence

Measurement of PD symptoms and characteristics in early life is in a nascent stage relative to PD assessment in adults. This measurement lag is both a cause and consequence of the overall lack of empirical attention historically paid to PD in early life, relative to empirical attention to PDs in adulthood (Tackett, 2010; Tackett et al., 2009). Certainly, empirical research on child and adolescent PD is hindered by lack of proper approaches to measurement, which should be considered a prerequisite to better understanding the etiology, phenomenology, developmental course, and clinical outcomes of early PDs (Tackett, Herzhoff, Reardon, Smack, & Kushner, 2014). With increased attention turning toward early PDs (as seen in multiple recent special issues devoted to this topic: e.g., Paris, 2013; Cicchetti & Crick, 2009; Stepp, 2012; Tackett, 2010; Tackett & Sharp, 2014), we can and should anticipate more sophisticated, thoughtful, and comprehensive approaches to measuring PD characteristics in children and adolescents, as well.

As with many areas of youth psychopathology, assessment of youth PD has traditionally relied on methods most commonly used in adult populations—specifically, structured diagnostic interviews and questionnaires completed by the parent, self, or clinician (Tackett, Herzhoff, Reardon, Smack, et al., 2014). Questionnaires include broadly based measures that cover a wide variety of personality disordered traits as well as more specific questionnaires designed to assess a narrowly defined domain (e.g., borderline: Crick et al., 2005, or narcissistic: Barry, Frick, & Killian, 2003, characteristics). Among broad, omnibus measure of PD traits, most involve adaptations of adult PD measures, with a recent focus on developing empirically based measures derived specifically for younger populations.

Omnibus questionnaire measures of PD characteristics have been frequently used in adult populations. Such measures possess a number of advantages, including their ability to measure multiple domains of PD characteristics simultaneously, efficiency, and low-cost of administration, and strong psychometric properties. A number of notable examples exist of adult PD questionnaires that have been modified in some way (e.g., for language and developmental appropriateness) to be used in younger age groups: the adolescent version of the Minnesota Multiphasic Personality Inventory, or MMPI-A (Butcher

et al., 1992; Sellbom & Jarrett, 2013), the adolescent version of the Dimensional Assessment of Personality Pathology, or DAPP-BQ-A (Tromp & Koot, 2008), and the youth version of the Schedule for Nonadaptive and Adaptive Personality, or SNAP-Y (Linde, Stringer, Simms, & Clark, 2013). Although—from a developmental standpoint—measures adapted down from adult use may not be ideal, these measures have served important functions in rapidly accelerating empirical research on early PD characteristics and facilitating continuity of findings across youth and adult samples. However, it remains important for measurement approaches for early PD to retain developmental sensitivity as well: those constructs relevant for adult PD may not all be relevant for youth and, likewise, some constructs relevant for youth PD may go unnoticed by researchers and clinicians working with adult PD.

Developmentally derived bottom-up measures highlight the need to examine empirically based PD constructs using different age groups as the *starting* rather than *ending* point. This approach allows developmentally relevant constructs to emerge, and less developmentally relevant constructs to recede, in the process of scale construction. The most prominent current example of such a measure is the Dimensional Symptom Itempool or DIPSI (De Clercq, De Fruyt, Van Leeuwen, & Mervielde, 2006). The DIPSI was constructed from raw data on child and adolescent populations, using items that emerged from the developmental literature as well as work on adult PDs. The higher order structure of the DIPSI comprises 4 domains: Disagreeableness, Introversion, Emotional Instability, and Compulsivity. Not only do these domains appear largely analogous to higher order factors from adult measures (e.g., the DAPP-BQ and the SNAP), but recent research suggests that these domains are hierarchically related to the SNAP-Y in meaningful ways and evidence both convergence and divergence with SNAP-Y scales (Kushner, Tackett, & De Clercq, 2013).

An issue that is not new to child psychologists of any domain is the conflict that emerges between a desire to collect multi-source, multi-informant data on our constructs of interest and the inevitable discrepancies that ultimately arise from different sources and different informants (Achenbach, McConaughy, & Howell, 1987). The area of youth PD is not immune to these broader concerns (Tackett, Herzhoff, Reardon, Smack, et al., 2014), as various informants and sources often correlate moderately, at best (Sharp, Mosko, Chang, & Ha, 2010; Tackett, Herzhoff, Reardon, Smack, et al., 2014). Furthermore, concerns over adult self-reports regarding PDs have previously resulted in researchers cautioning against sole reliance on self-report of PD, even at older ages (Klonsky, Oltmanns, Turkheimer, 2002; Oltmanns & Turkheimer, 2009). Indeed, recent empirical research using both parent and youth self-report have pushed back against the idea that self-report may serve as a gold standard for PD measurement: in one study, parent reports of youth PD traits moderated hormonal associations with psychopathology, but youth self-reports of PD traits did not (Tackett, Herzhoff, Josephs, Harden, & Page-Gould, 2014). More explicit efforts to disentangle informant discrepancies for youth PD are beginning to emerge (Tackett, Herzhoff, Reardon, Smack, et al., 2014), but much more work is needed to fully understand how best to integrate information from multiple sources and multiple informants in the assessment of youth PD. In the meantime, we encourage researchers and clinicians to collect multi-method, multi-informant data when possible but retain a more nuanced approach to integrating information as opposed to reductionist methods of aggregation (e.g., creating averages across informants). Not only does each method and source potentially contain valuable information, but the discrepancies among them may also be useful and predictive of later outcomes (e.g., De Los Reyes, 2011; Tackett, Herzhoff, Reardon, Smack, et al., 2014).

Measurement Issues in Later Life

Turning to measurement issues for PDs at older ages, it is important to consider those fundamental measurement issues in the assessment of PDs which exist across all age groups—not just later life. These measurement problems impede our understanding of PDs and personality pathology in general. One problem is that the diagnostic thresholds—the number of criteria needed to meet diagnosis of a PD—are imperfect markers of personality pathology and somewhat arbitrary (Clark, 1992; Hyman, 2002; Livesley, Schroeder, Jackson, & Jang, 1994; Oldham, 2007). Why are patients eligible for a diagnosis of avoidant PD when they meet 4 of 7 criteria but not 3 of 7? Another fundamental measurement issue that limits our understanding of PDs in general has to do with the general approach that is used to assess PDs. Currently, much of the field uses a categorical approach to identifying the PD—one is either categorized as having or not having a PD based partly on the number of criteria they meet (Krueger, Skodol, Livesley, Shrout, & Huang, 2007). However, there is good evidence to suggest that personality pathology might be best described dimensionally (a person has degrees of PD pathology), rather than

categorically (the person either does or does not have a PD). We will return to these two fundamental assessment issues—the issues of thresholds and a categorical vs. dimensional approach— later in the chapter and describe how they are particularly problematic for studying PD in late life. Next, we describe additional measurement issues in assessing PDs. We comment on how each of these measurement issues make difficult the assessment of PDs across all age groups, and how some of these measurement issues are particularly marked for assessing PDs in later life.

We briefly noted that there are conceptual problems with using thresholds to categorize people as either having a PD or not, but there are additional problems with the criteria themselves that are particularly troublesome when applied to individuals entering later life. The criteria for meeting each PD were created with a younger adult in mind (Mroczek et al., 1999; Segal et al., 2012). When applied to older adults, the items have relatively poor face validity. Several of the problematic items have been described elsewhere (Rosowsky, Abrams, & Zweig, 1999), but one example comes from the criteria for avoidant PD. One criterion for meeting avoidant PD is that the person, "*avoids occupational activities*. . . " (APA, 2000, p. 721). This item may work well enough to identify avoidance in a younger adult, but in an older, retired adult it does not work as well. A younger adult with severe avoidant PD pathology might endorse this item for reasons having to do with the person's PD. In contrast, an older adult with a similar level of avoidant PD pathology might not endorse the item because the older adult is retired. This means that an older adult could respond negatively to all probes like this one that are designed to assess the PD pathology, simply because of the context of the probe—having to do with occupational activities—that no longer applies to the older adult. Because of problems with this and other items, one could gain an inaccurate picture of an older adult's level of PD pathology. In larger research studies of many older adults, one might incorrectly infer that avoidant PD pathology decreases in older adults, simply because they are less likely to endorse some items because of their age (Balsis, Woods, Gleason, & Oltmanns, 2007).

The problems with face validity do not solely reveal themselves for the diagnosis of avoidant PD, but they are pervasive across many of the 79 diagnostic items (Segal et al., 2006). Items such as the one for schizoid PD, "has little . . . interest in . . . sexual experiences with another person" (APA, 2000, p. 697), may also fail to capture PD pathology in older adults. Whereas this item might be strongly related to schizoid PD pathology in younger adults, it might be less strongly related to schizoid pathology in older adults. A younger adult who endorses this item might have high levels of schizoid PD pathology. Because there are not many obvious alternative explanations for why the person might endorse this item (that would not apply to all other age groups), the relationship between the construct of interest and endorsement of this item in this age group is strong. For older adults, however, the relationship might be more tenuous. An endorsement might represent side effects of medications, physiological changes that prevent certain sexual capacities, different hormonal levels, or even lack of partner availability. So for older adults, an endorsement of this item might be related to schizoid PD, but it also might be related to a number of other age associated factors.

In addition to these specific examples, a recent study revealed that approximately half of the PD criteria may contain measurement bias across younger and older age groups (Balsis, Gleason, et al., 2007). A follow-up study revealed that the measurement bias may actually lead to problems diagnosing similar levels of PD severity across individuals from different age groups (Balsis, Woods, et al., 2007). Thus, problems with poor face validity can lead to failures to diagnose personality pathology in older adults (Zweig & Parchi, 2010). Poor face validity can also lead to other measurement errors. For example, having items with poor face validity means that a measure will have poor internal consistency as indicated by alpha reliability. If the PD criteria have high face validity for younger adults, then the ratings across items will likely reflect the core dimension of interest and alpha reliability may be relatively high. However, if the PD criteria have relatively poor face validity, as is the case for older adults, then ratings across items will be less likely to reflect the core dimension of interest. If this is the case, then the alpha reliability of the measure will be lower. Similar problems arise with inter-rater reliability and different aspects of validity.

A recent study examined all 79 diagnostic criteria (plus criteria for provisional PDs) across the adult life span, and reported changes for those criteria between approximate ages 20 and 50 (Gutiérrez et al., 2012), suggesting that PDs change with age. The table in the article (p. 769) shows the items ranked in order from the ones that showed the greatest decrease across progressive age groups to the ones that showed the greatest increase across progressive age groups. While these data have been taken as evidence that PD

features change with age, an examination of the extreme items (the greatest decreasing items and greatest increasing items) suggests that these items are likely picking up on changes in age rather than changes in PD pathology. For example, three of the five items with greatest increase in endorsement with age are schizoid items. The two with the greatest increases are "No close friends" (p. 769) and "No interest in sex" (p. 769), an increase in these endorsements probably do not reflect an increase in people becoming more schizoid in middle age, but simply a reflection of that context of middle adult life relative to the context of early adult life. The other items among the top five that increased with age were for obsessive-compulsive PD. These items were workaholism (p. 769) and stinginess (p. 769). Here again an increase in the likelihood of endorsing these items with age seems to reflect more about that person's life circumstance during middle age rather than an increase in obsessive-compulsive PD pathology. Increases in these items then drive the increase in diagnosis of these two disorders (schizoid and obsessive-compulsive PD), making it appear as though people are changing in terms of their PD pathology along these dimensions. Instead, it is likely the case that endorsement of these items (and the apparent increase in pathology) along these two dimensions merely reflects changes in life stage.

On the other end of the spectrum are the items that were endorsed less frequently with age. Five of the first six are items for antisocial PD, which corresponds with the dramatic decrease in antisocial PD diagnoses into middle adulthood and later life. For example, the item about having reckless disregard for one's safety is endorsed less often as people age, but here again one might consider the possibility that people with antisocial PD adopt different strategies as they age to express their antisocial personality pathology (see Oltmanns & Balsis, 2011 for a relevant case study). The PD item with the biggest change is the one for narcissistic PD, Fantasizes about unlimited success. People who are older are less likely to endorse this item, but here again, this decreased endorsement might not represent a change in baseline narcissism, but rather a reconstitution of it. Older narcissists might be less likely to *look forward* and fantasize about *future* successes than younger narcissists simply because of their advanced age. Instead, older narcissists may reinterpret their current life's circumstance (regardless of how rosy it is) as evidence of success. The overall findings from this paper (Gutiérrez et al., 2012) showed an overall decrease in PD pathology. However, we suggest that this overall trend may simply reflect a problem with the criteria. Unfortunately, data that appear to show a mellowing or a decrease in PDs in late life create the perception that PDs aren't important in later life, which may have the unfortunate consequence of keeping researchers from examining PDs disorders in later life.

Thus, we have seen how many of the criteria may not work well for measuring PDs in later life. One solution is to rewrite the items for older adults. This would mean that younger adults would have one set of diagnostic criteria and older adults would have a different set. At a certain age, which would be difficult to define, a clinician would opt to use the later life diagnostic criteria. Having two different sets of criteria is a tempting proposition, but introduces multiple problems such as meaningful longitudinal comparison, determining the age at which criteria sets would switch, and the need to recognize that older adults are but one example of special populations and creating alternative item sets for multiple groups is not feasible.

Another solution is to retain the individual items but weight them differently across age groups. This means that one would apply the same items to younger adults and older adults, but weight the responses according to the ability of those items to differentially identify the latent trait across the age groups. Clinicians could enter into a computer or a personal digital assistant (PDA) the age of the participant (and other demographic variables for more sophisticated weights that take into consideration different demographic influences on item function) as well as the pattern or symptoms for that individual, and the software could instantly reference the literature and report to the clinician where the client stood along the given dimension of interest. The dimension could potentially be calibrated to be identical across members of different age groups, ethnicities, genders, or other variables (for example, inpatient vs. outpatient). This is a potentially viable solution that would ameliorate measurement problems for older adults and bring a certain degree of consistency to PD measurement that has not been observed previously.

A third solution is to consider PDs at another level of analysis. The *DSM* criteria operate at a very contextually rich behavioral level; "avoids occupational activities," "has recurrent suspicions . . . regarding fidelity of spouse or sexual partner," and " . . . aggressiveness, as indicated by repeated physical fights or assaults" are such examples. Each of these items describes a personality style or response that reflects a personality trait in action in a particular context. As we described earlier,

many of the *DSM* items lack face validity for use with older adults because they tend to include a younger adult context in their wording. Therefore, one may be able to circumvent this problem by using items that do not contain any context. The item, "avoids occupational activities" would simply become, "is avoidant." Similarly, the item, "has recurrent suspicions . . . regarding fidelity of spouse or sexual partner," could become "is suspicious," and " . . . aggressiveness, as indicated by repeated physical fights or assaults" could become, "aggressive (broadly defined)." A likely consequence of such a change would be decreased reliability of symptom-level measurement, but it remains an important alternative to consider.

A trait approach to understanding PDs might be the right level of analysis, as traits tend not to be linked as strongly to any particular context and have more advantages in developmental research, as previously discussed in this chapter. Researchers have argued that existing measures designed to assess personality traits are sample invariant across age—that they measure the traits equally well in younger and older adults (see Allemand, Zimprich, & Hendriks, 2008). While this possibility of using existing trait measures to examine personality pathology across the life span seems appealing, a close look at some of the extant literature reveals at least relatively small measurement imprecision. With that small caveat in mind, the broader trait measures clearly show many fewer measurement problems across age groups and over time (Allemand, Zimprich, & Martin, 2008). Items on an ideal measure would be vetted for invariance *before* the measure becomes available to the community of researchers. We next turn to discussing core cross-cutting components of PDs—traits, emotions, relationships, and identity—in early and later life.

Components of PD

Traits: Early Life

As mentioned earlier, both abnormal and normal personality traits can be reliably assessed during childhood (e.g., Paris, 2003; Rothbart & Bates, 2006), are moderately stable during this early developmental period (e.g., Roberts & DelVecchio, 2000; Stepp et al., 2010), and their stability is largely heritable (e.g., Bornovalova et al., 2009; De Fruyt et al., 2006). These similarities, along with the finding that abnormal personality changes *follow* changes in normal personality in adults (Warner et al., 2004), underline the important role that traits play in the early development of PDs. In fact, PD preventions targeting youth based on their normal personality traits have already shown great utility in diminishing the development and severity of adolescent PDs (e.g., Chanen et al., 2008). PD counts based on the FFM of normal personality have also shown discriminant validity in screening PDs and psychopathy in youth (Decuyper, De Clercq, De Bolle, & De Fruyt, 2009). Despite their key role in defining PDs, abnormal personality traits have been distinguished from PDs by emphasizing two additional components needed to conceptualize PDs beyond abnormal traits (Livesley & Jang, 2000; Verheul et al., 2008). Specifically, PDs involve dysfunctional cognitions about the self and others (Fonagy & Bateman, 2008) as well as interpersonal dysfunctions, both of which we discuss later, and which are not typically well-represented in trait models (normal or abnormal). Here, we broadly summarize findings on relationships between traits and PDs in youth by considering contributions from normal personality traits, omnibus abnormal personality trait models (e.g., DAPP-BQ, DIPSI), and additional narrowly defined traits that have been connected to youth PD (e.g., callous/unemotional traits).

A limited number of studies have investigated the relationship between normal personality traits and Cluster A features. Of the studies that have investigated correlates of Cluster A features, most have found that Cluster A features are associated with characteristics such as odd speech (Carlson & Fish, 2005), having unusual fantasies (Wolff, 1991), showing unconventional verbal responses (Caplan, 1994), and holding paranormal beliefs (Hergovich, Schott, & Arendasy, 2008). In FFM terms, these characteristics could arguably be summarized under the personality trait openness to experience. Other studies have also found youth Cluster A features to be associated with an absence of close friends, suspiciousness (Carlson & Fish, 2005), being described as loners (Wolff, 1991), and experiencing paranoia (Rutter, Kim-Cohen, & Maughan, 2006), potentially suggesting lower scores on the FFM trait extraversion or agreeableness. In fact, in a sample of adolescents, at the higher order personality trait level, Cluster A PD symptoms have been most consistently linked with low agreeableness and low extraversion (De Clercq & De Fruyt, 2003; De Clercq, De Fruyt, & Van Leeuwen, 2004). Interestingly, only schizotypal PD symptoms were found to show positive relationships with the higher order openness factor (De Clercq & De Fruyt, 2003; De Clercq et al., 2004) whereas schizoid PD symptoms were negatively associated with openness and paranoid PD symptoms showed no associations (De Clercq & De Fruyt, 2003), suggesting divergent associations among Cluster A PDs.

More studies have investigated the relationship between normal personality traits and Cluster B personality disorders; therefore, we will summarize findings separately for psychopathy, narcissism, and borderline PDs. With regard to psychopathy, studies have found that personality correlates of psychopathy in early life mirror those in later life (De Clercq & De Fruyt, 2003; De Clercq et al., 2004; Lynam et al., 2005; Salekin, Leistico, Trobst, Schrum, & Lochman, 2005). Specifically, at the higher order personality trait level, psychopathy is associated with low agreeableness and conscientiousness as well as high neuroticism in adolescence. Furthermore, at the lower order trait level, psychopathy is also associated with low inhibition—indicating low conscientiousness—as well as high activity, dominance and sociality—indicating high extraversion—and high coldness and low compliance—indicating low agreeableness—(e.g., Glenn, Raine, Venables, & Mednick, 2007; Le Corff & Toupin, 2010). Furthermore, in contrast to adults, associations between psychopathy and anxiety or fearfulness seem to be more fluid in early years, with psychopathy characteristics being longitudinally associated with low fearfulness in early childhood (Glenn et al., 2007) but with high anxiety in adolescence (Salekin, Rosenbaum, & Less, 2008), and overall questions remaining regarding the nature of youth psychopathic traits in the context of anxiety.

With regard to narcissism, studies have found that—like other Cluster B disorders—it is associated with high aggression (Barry, Grafeman, Adler, Pickard, 2007)—indicating low levels of agreeableness. At the lower order personality trait level, narcissism is negatively associated with all agreeableness facets but positively associated with achievement striving yet negatively with concentration and perseverance—indicating diverse connections with conscientiousness facets (De Clercq & De Fruyt, 2003; De Clercq et al., 2004). More variability has been found in the association with self-esteem—indicating neuroticism—with some studies finding associations with low self-esteem and others finding no association (Barry et al., 2003; Barry, Thompson, et al., 2007; Thomaes, Stegge, Bushman, Olthof, & Denissen, 2008). These differences have led to suggestions that the association might change over time to the positive association typically found in adulthood (Barry, Grafeman, et al., 2007). In addition, associations between self-consciousness and narcissism may change depending on the extent to which comorbidity is accounted for. Specifically, when relevant personality facets were entered simultaneously to predict narcissism without partialling out comorbid psychopathology, self-consciousness was a positive predictor; however, when general psychopathology was partialed out, self-consciousness was a negative predictor, suggesting that low self-consciousness has a unique relationship with specific variance in narcissism (De Clercq & De Fruyt, 2003).

Most studies investigating the relationship between normal personality traits and PDs in youth have focused on borderline PD. All dysfunctional aspects of borderline PDs (i.e., relationship difficulties, identity disturbance, impulsivity, and affective instability) have been associated with normal personality traits although with different levels of coverage. Specifically, at the higher order personality trait level, relationship difficulties can be captured by low agreeableness, identity disturbance can be captured by low self-confidence and high Egocentrism, and impulsivity can be captured by low conscientiousness, whereas affective instability can be captured by high neuroticism (Tackett & Kushner, 2014). In fact, low agreeableness, conscientiousness, and extraversion, as well as high neuroticisms have been most consistently associated with borderline PD (e.g., De Clercq et al., 2004; Saulsman & Page, 2004). Overall, of the borderline PD dysfunctions, impulsivity seems to be best captured by normal personality traits whereas identity disturbance seems to be captured most poorly. At the lower order personality trait level, depression, impulsiveness, vulnerability, anxiety, and low self-confidence (indicating neuroticism), low trust, irritability, and low compliance (indicating agreeableness), and low persistence (indicating conscientiousness) have been found to predict borderline PD symptoms in youth over and above comorbid psychopathology (De Clercq, De Fruyt, & Mervielde, 2003; De Clercq et al., 2004). Furthermore, sensation seeking in childhood has also been related to borderline PD (Gratz et al., 2009), potentially explaining the increased risk of sexually transmitted diseases and other health issues that have been associated with the disorder (Chanen, Jovev, & Jackson, 2007). In terms of early temperament, both high activity—indicating extraversion—and high emotionality have been related to borderline PD (Carlson, Egeland, & Sroufe, 2009).

Many fewer studies have investigated the relationship between normal personality traits and Cluster C PDs. In fact, controversy exists over whether avoidant PD can even be clearly differentiated from social phobia in adolescence (Rettew, 2000). Of the studies that have investigated correlates of Cluster C PDs, most have found that adult avoidant PD is associated with diminished involvement in extracurricular activities, including athletics and other hobbies, as

well as diminished popularity, including a smaller number of positive relationships with adults, in childhood and adolescence—indicating low extraversion (Rettew et al., 2003; Skodol et al., 2002). In fact, at the higher order personality trait level, Cluster C PDs have been found to be most consistently associated with low extraversion and high neuroticism as well as with low Openness to Actions at the lower order personality trait level (De Clercq & De Fruyt, 2003). In addition, obsessive-compulsive PD shows strong associations with conscientiousness and its maladaptive variant Compulsivity even after partialling out comorbid psychopathology (Aelterman, Decuyper, De Fruyt, 2010). In terms of early temperament, increasing withdrawal, a possible predictor of avoidant PD, has been found to be most consistently associated with low resiliency, i.e., the inability to quickly adapt to changes in the environment (Eggum et al., 2009).

Normal personality traits can also be affected by maltreatment in childhood to take on pathological profiles. Specifically, childhood abuse has been linked with personality profiles that were lower in openness, conscientiousness, and agreeableness and higher in neuroticism and this maladaptive profile was relatively stable over a three-year period (Rogosch & Cicchetti, 2004). More generally, childhood maltreatment—including abuse of physical, sexual, and verbal nature, as well as neglect—has been linked with higher rates of PDs (Cohen, Crawford, et al., 2005; Guzder, Paris, Zelkowitz, & Marchessault, 1996; Johnson et al., 2001; Raine, 2006; Skodol et al., 2005; Zanarini et al., 2005). The mechanism by which this link operates seems to be maladaptive parenting succeeding the maltreatment in combination with other endogenous risk factors (Fonagy & Bateman, 2008).

Many PD measures assess a broad range of abnormal personality traits (Widiger & Simonsen, 2005), as previously described in this chapter. Similar to omnibus models of normal personality traits, these omnibus models of abnormal personality traits typically converge on analogous factor structures (e.g., Clark, 1993; De Clercq et al., 2003; Livesley & Jackson, 2009). Specifically, at the higher order trait level, omnibus models of abnormal personality traits usually include the four factors Emotional Instability, pathological Introversion, Antagonism, and Compulsivity and sometimes a fifth factor labeled Peculiarity or Psychoticism that captures Cluster A characteristics (Harkness & McNulty, 1994; Tackett, Silberschmidt, Krueger, & Sponheim, 2008). Studies using the Dimensional Assessment of Personality Pathology-Basic Questionnaire for Adolescents (DAPP-BG-A; Tromp & Koot, 2008) have found that the model's higher and lower order traits are related to *DSM-IV* PD symptoms in hypothesized directions. Specifically, referred adolescents with PDs scored higher on 11 of the 7 lower order scales and two of the four higher order scales compared with nonreferred adolescents, with the facets self-harm, identity problems, and emotional dysregulation showing the greatest effect. In terms of distinguishing between classes of adolescents referred for PDs and those referred for other problems, the scales self-harm, emotion dysregulation, suspiciousness, conduct problems, and dissocial behavior performed particularly well. Furthermore, similar to the incremental validity that normal personality trait facets show in the prediction of PDs (e.g., Reynolds & Clark, 2001), abnormal personality trait facets also showed incremental validity in predicting all PD symptoms, except for schizoid, schizotypal, and passive-aggressive PD symptoms.

Specific PD traits, such as callous-unemotional traits, have been conceptualized as a key component of psychopathy in youth alongside egocentricity and impulsivity (Barry et al., 2000; Salekin & Frick, 2005) and have been found to discriminate between youths scoring below or above clinical psychopathy cutoffs based on the FFM (Decuyper et al., 2009). Callous-unemotional traits in early life also predict psychopathy in adulthood (Burke, Loeber, & Lahey, 2007). Associations between callous-unemotional traits and omnibus models of abnormal as well as normal personality are similar to those associations with adult psychopathy, supporting the key role that those traits play in youth psychopathy (Decuyper, De Bolle, De Fruyt, & De Clercq, 2011; Latzman, Lilienfeld, Latzman, & Clark, 2013). Specifically, callous-unemotional traits are most consistently associated with low agreeableness/high Antagonism, and low conscientiousness/Compulsivity. Associations with neuroticism/Emotional Instability differed across studies, with a boys-only sample showing high neuroticism/Emotional Instability in relation to callous-unemotional traits (Latzman et al., 2013) and the mixed-gender sample showing low neuroticism/Emotional Instability in relation to callous-unemotional traits (Decuyper et al., 2011). In addition to associations with psychopathy, callous-unemotional traits have also been associated with high borderline and low sadistic traits, with self-serving cognitive distortions such as blaming others (e.g., Chabrol, van Leeuwen, Rodgers, & Gibbs, 2011), and with low reward and punishment responsivity (Marini &

Stickle, 2010). Additionally, although both normal and abnormal personality traits predict unique variance in callous-unemotional traits, callous-unemotional traits showed incremental prediction of general psychopathology symptoms in a large community sample (Moran et al., 2009). Thus, normal and abnormal personality traits clearly play a critical role in the manifestation, development, and outcomes associated with personality pathology in early life.

Traits: Later Life

Numerous studies suggest that significant relationships exist between the five-factor model of personality (i.e., neuroticism, extraversion, openness, agreeableness, and conscientiousness) and the *DSM-IV-TR* PDs in adults. Specifically, in a meta-analysis, Saulsman and Page (2004) found that neuroticism was positively related and agreeableness was negatively related to many PDs, with the neuroticism factor showing the highest mean correlation with PD categories. As stated elsewhere in this chapter, self-reported neuroticism/negative affect may decrease across the life span (Roberts et al., 2006; Mrozcek & Kolarz, 1998), but there is evidence that those who score high on neuroticism follow a different trajectory. Rather than decrease with age, high-scorers in neuroticism are less likely to experience the positive changes that frequently accompany the aging process (see Charles & Carstensen, 2009). In other words, individuals who score high on neuroticism likely remain high on neuroticism, even into old age, which could have implications for later PD stability and impairment.

It could also be that the age-related decline of neuroticism and negative affect is simply an artifact of the aging process. As individuals age, their life contexts change, such that they likely spend more time alone due to retirement, the empty nest, the potential death of spouses, and declines in physical abilities which prevent mobility. In this lower activity context, an older individual may not feel particularly neurotic or disagreeable, and therefore not report it. In social situations or engagement with the healthcare system, however, these latent personality attributes will likely reemerge. So, it may not be that individuals actually decrease in neuroticism and increase in agreeableness, as the observed data suggests, but that the context of older adulthood changes to make the experiences of these traits less frequent and less salient for older adults, and when life events present themselves, their latent pathology will reemerge. Thus, traits remain a critical component of PD development across the life span.

Emotions: Early Life

Another component that plays an important role in the early development of PDs is emotion and emotion regulation. Emotion dysregulation can be described as a person's inability to modulate the duration, intensity, or timing of their emotions. That is, rather than referring to the content of emotion, emotion dysregulation describes a person's response to their emotions (e.g., Gratz et al., 2009). Different PDs in youth have been hypothesized to be associated with different forms of dysregulated emotions. Specifically, Cluster B PDs have been hypothesized to be characterized by underregulated emotions, Cluster C PDs by overregulated emotions, and Cluster A PDs by a general lack of emotional responses (Shiner & Tackett, 2014). Empirically, for instance, the Cluster B borderline PD has been linked with rage and a tendency to feel overwhelmed by emotions (Reich & Zanarini, 2001) whereas the Cluster A schizophrenia spectrum has been characterized by constricted affect in childhood and adolescence (Carlson & Fish, 2005). Despite these hypothesized links between emotions and PDs across clusters, most empirical research on youth emotions has focused on links with borderline PD, with fewer studies focusing on psychopathy and almost none on other PDs in childhood and adolescence. Therefore, we focus here mainly on summarizing findings on the relationship between emotions and borderline PD, as well as psychopathy.

Borderline PD has been most strongly linked with emotion dysregulation in childhood and adolescence. In fact, structural models of borderline PD in youth include affective instability as one of the disorder's defining components (Becker, McGlashan, & Grilo, 2006) and Linehan (1993) postulates that most borderline PD symptoms are caused either directly or indirectly by dysregulated emotions or maladaptive attempts to modulate emotional reactions. Empirically, moodiness in infancy, emotionality and emotional sensitivity in early childhood, and emotional instability in middle childhood and adolescence have all been associated with later borderline PD symptoms in adulthood (e.g., Carlson et al., 2009; Crick et al., 2005; Goodman et al., 2010). Retrospective reports suggest that adults with borderline PD had greater difficulties with emotion regulation in their early years than did adults with other PDs (Reich & Zanarini, 2001). Compared with adults, children experience emotions such as anger and moodiness (that have been associated with borderline PD) more frequently (Zanarini et al., 2011).

Despite self-reported greater emotional sensitivity in childhood, adolescents with borderline personality pathology appear to be no more accurate at identifying emotions than are healthy controls (Jovev et al., 2011). In fact, alexithymia—the tendency to have difficulty identifying and describing emotions (e.g., Taylor, Bagby, & Parker, 1997)—has been found to mediate the link between early attachment disruptions and the development of borderline PD in adolescence (Deborde et al., 2012). Such early attachment disruptions may provide children with inadequate opportunities for the development of emotion regulation (including accurately identifying emotion), which in turn increases a child's likelihood of developing borderline PD later in life (Fonagy & Bateman, 2008). Emotion dysregulation also partially mediates the effects of affective dysfunction in girls (but not in boys; Gratz et al., 2009) and theory of mind (Sharp et al., 2011) on borderline PD symptoms in youth. Interestingly, despite the important mediating role of emotion dysregulation for links between borderline PD features and symptoms, youth with borderline PD regulate their emotions no differently than healthy controls after a mild interpersonal rejection (Lawrence, Chanen, & Allen, 2011). Compared with healthy controls, though, youth with borderline PD reported more intense mood states across a range of negative and positive mood states, which suggests higher risk for experiencing emotions that are too intense to be effectively regulated (Lawrence et al. 2011).

Borderline PD and Cluster C PDs are linked with attention biases toward negative emotional words in adulthood (Arntz, Appels, & Sieswerda, 2000), suggesting that a hypersensitivity to negative emotion stimuli might be a cross-cutting factor underlying multiple PDs. In contrast, in adolescence, borderline PD has been associated with attention biases to negative emotional faces only when adolescents were in a negative mood, whereas it was associated with the reverse bias when the same adolescents were in a positive mood (von Ceumern-Lindenstjerna et al., 2010), underlining the importance of taking into account those individuals' current emotional state. At a neurological level, a smaller anterior cingulate gyrus—a brain area involved in gauging the importance of emotional stimuli as well as regulating emotions—has been associated with borderline PD in adults (Hazlett et al., 2005; Tebartz van Elst et al., 2003) as well as borderline PD and major depressive disorder comorbidity in adolescents (Goodman et al., 2011). Thus, emotions and emotion regulation clearly play a critical role in the development of borderline PD in early life, although more research is needed to fully understand the relations between these domains.

Compared with borderline PD, fewer studies have investigated the link between emotion and emotion dysregulation with youth psychopathy, although emotion has long been considered a core component in theoretical approaches to early psychopathy. Psychopathy is conceptualized as reflecting decreased emotional responses (Blair, Peschardt, Budhani, Mitchell, & Pine, 2006) and, as mentioned earlier, callous-unemotional traits have been conceptualized as a defining feature of psychopathy in children and adolescents (Frick & White, 2008). In a more recent study, however, researchers found that decreased response was specific to fearful emotions and did not generalize to other types of emotions, which is in line with links between psychopathy and impoverished fear learning, physiological responses to fearful stimuli, and identification of fear in peers (Marsh et al., 2011). For example, psychopathy has been associated with decreased electrodermal activity in response to distressing and threatening visual stimuli in children (Blair, 1999) and distressing white-noise bursts in adolescents (Fung et al., 2005).

Emotions: Later Life

Although results have sometimes been mixed, research has generally supported the conclusion that reported experiences of positive affect slightly increase across the adult life span and reported experiences of negative affect generally decrease across the adult life span (Carstensen, Pasupathi, Mayr, & Nesselroade, 2000; Mrozcek & Kolarz, 1998). Research also suggests that positive emotional experiences last longer and negative emotional experiences last for a shorter duration for older adults than younger adults (Carstensen et al., 2000). Additionally, John and Gross (2004) suggest that emotion regulation strategies generally improve with age, with older adults using more adaptive strategies (see also Carstensen, Fung, & Charles, 2003) and fewer maladaptive strategies to regulate their emotions. Like with personality traits, therefore, for the population in general it appears that the emotional lives of adults improve with age (e.g., Carstensen & Charles, 1998; Gross et al., 1997).

Contrary to this somewhat rosy picture, those with PDs likely experience as much or more negative emotions in later life and have more difficulty regulating their emotions than their normal counterparts. Charles and Carstensen (2009), for example, report that individuals who are high on neuroticism "do not experience age-related benefits in emotional functioning" that are frequently found to be characteristic of older adults (p. 399). As many PDs

are associated with neuroticism (Saulsman & Page, 2004), individuals with PDs are perhaps among the ones who do not experience the aforementioned age-related emotional benefits. This finding makes intuitive sense, as one might expect those with PDs to have a relatively difficult time learning from their previous socio-emotional experiences. Such individuals may not be able to optimize their emotional experiences like people with adaptive personality structures.

Interpersonal Relationships: Early Life

The third core component that plays an important role in the early development of PDs is interpersonal relationships. Indeed, the interpersonal context in which behavior arises has been proposed as one element (in addition to identity disturbances) that clarifies the difference between normal personality traits and PDs (Livesley & Jang, 2000; Verheul et al., 2008). Research on interpersonal relationships in PDs has focused primarily on two interrelated but distinct constructs: attachment and social cognition. Therefore, we focus here mainly on summarizing findings on links between attachment, social cognition and PDs. More recent research has also pointed to the importance of relational aggression in early personality pathology, so we will briefly discuss this here as well.

Attachment to a primary caregiver has been conceptualized as a mental representation of the child's relationship, environment, experience, and self (Shiner, 2010), that predicts adaptive and maladaptive trajectories and might explain later personality disordered behavior (Shiner & Tackett, 2014). Specifically, the representation of the child's early relationship with their primary caregiver is hypothesized to serve as a template for the child's future relationships and responses to their environment (Hazen & Shaver, 1987; Mikulincer & Shaver, 2007; Shiner & Tackett, 2014). Two dimensions of attachment have been identified by contemporary attachment theorists: (1) a person's preference for affiliation versus independence and (2) a person's tendency to feel secure or worried about a partner's availability (Fraley & Shaver, 2008). Adaptive attachment typically develops in infancy and early childhood, when children form patterns of insecurity and security based on their relationship with their primary caregiver (Mikulincer & Shaver, 2007). Consequently, infancy and early childhood are critical developmental periods for PDs (Tackett et al., 2009), consistent with the notion that PDs emerge early in life (Paris, 2003).

Although disrupted attachment is likely an important component in the development of many different kinds of PDs, theory and research has focused especially on its importance for the development of borderline PD (Levy, 2005; Westen, Nakash, Thomas, & Bradley, 2006). For example, adolescents with borderline PD have a higher prevalence of maladaptive attachment styles that include rejection and abandonment fears (Westen et al., 2006). Similarly, young children of mothers who have borderline PD represent the attachment with their parents in a more maladaptive way (Macfie & Swan, 2009). Specifically, these children narrate stories that include more negative expectations about the relationships with their parents, more abandonment fears, and more reversed roles between parents and children, than do children with mothers without borderline PD. In addition, attachment disorganization and maternal hostility in early childhood predict borderline PD symptoms later in adulthood (Carlson et al., 2009). More specifically, this association may be mediated by disturbances in youth's self-representation (Carlson et al., 2009) as well as alexithymia, the inability to identify emotions, in adolescents (Deborde et al., 2012). Maternal separation in early childhood also predicts both increases in borderline PD symptoms throughout adolescence and adulthood, as well as slower decreases in these symptoms over time, and this effect occurred over and above other risk factors such as abuse, risky parenting, and maternal problems (Crawford et al., 2009). Thus, theory and research converge on the importance of attachment for PD development in early life, although more empirical research is needed, especially research exploring other manifestations of early PDs beyond borderline PD.

In addition to the importance of attachment in the development of PD, researchers have also broadened their focus of self-other cognitions that affect the development of PDs. Examples of such self-other cognitions that affect children's interpersonal adjustment or maladjustment include beliefs around how flexible their own behavior is, perceptions of others' intentions, perceptions of their self-competence, and experiences of alienation from their peers (Shiner, 2009; Tackett et al., 2009). Specifically, interpersonal problems for people with PDs often arise because they misperceive others' motives and emotions (Tackett et al., 2009). In other words, they have difficulty empathizing with others and using the knowledge gained from empathy to guide their behavioral responses. Examples of misperceptions of others' motives might include unreasonable abandonment fears in dependent PD or paranoid beliefs about other people in paranoid PD. Interpersonal problems for people with PDs also often arise because they misperceive the nature of their relationships with other

people and consequently misjudge the appropriateness or inappropriateness of their own behavior (Tackett et al., 2009). For example, individuals with PDs might maintain too much or too little distance from other people, for instance, in relationships with romantic partners. In addition, their rigidity and inflexibility can often worsen their interpersonal problems because people with PD have difficulty adapting to social challenges (Westen & Heim, 2003).

Especially relevant for the development of a diverse variety of personality pathology in youth are the following three components of social cognition: (1) trust, (2) theory of mind (or mentalizing), and (3) emotion recognition (Sharp, 2012a). For example, in youth, hypomentalizing has been associated with antisocial PD, whereas hypermentalizing has been associated with borderline PD (Sharp, 2012b). In an adolescent sample, the relationship between borderline personality traits and hypermentalizing (i.e., over-interpreting others thoughts and motives) was mediated by emotion regulation (Sharp et al., 2011). Deficits in social cognition, such as differentiating and integrating one's self perspective with others', is also associated with borderline PD in adolescence and early adulthood, over and above attachment disturbance (Jennings, Hulbert, Jackson, & Chanen, 2012). These deficits generalized across social situations and were not specific to those that are most relevant to borderline PD, such as situations of abuse, deprivation, or abandonment.

Apart from borderline PD, deficits in self-other cognitions are also relevant to the development of other PDs. For example, although some studies have found that children with psychopathic traits have a normative number of friends, they have also found that those children perceived conflict in their friendships more so than their partner did, suggesting that children with psychopathic traits might be biased in their social-cognitive processes (Muñoz, Kerr, & Bešic, 2008). Despite these biases, friendships were still found to be protective against delinquent behavior in children with psychopathic features. Furthermore, in the case of narcissistic tendencies, differences in children's motives have distinguished between adaptation and maladaptation, where children with communal motives (e.g., motivations toward affiliation and altruism) tend to have adaptive self-esteem whereas children with agentic motives (e.g., motivations toward power and autonomy) tend to have high self-esteem marked by maladaptive narcissistic tendencies (Thomaes et al., 2008). Finally, positive schizotypy has been negatively associated with theory of mind performance, but persecutory delusions and impulsivity were positively associated with theory of mind performance in adolescence (Barragan, Laurens, Navarro, & Obiols, 2011). The role of social cognitive processes remains an important area for future research in early PD development.

Relational aggression (also referred to as social or indirect aggression) is aggressive behavior intended to damage one's social status or interpersonal relationships (Crick & Grotpeter, 1996). The role of both perpetrator and victim in the context of relational aggression appears to be important in the development of PDs, most notably borderline PD. In fact, relational aggression has been conceptualized as an early indicator of borderline PD (Crick et al., 2005; Rogosch & Cicchetti, 2005), although recent research suggests it may be more central to externalizing PDs broadly conceived and show some specific links to narcissistic tendencies (Tackett, Herzhoff, Reardon, De Clercq, & Sharp, 2014). Engagement in social and physical aggression in middle childhood predicts borderline (and narcissistic) personality features in adolescence, regardless of whether these forms of aggression generally decreased with age (Underwood, Beron, Rosen, 2011). Beyond typical externalizing PDs, adolescents with paranoid PD increase faster in their use of peer bullying from childhood to adolescence, suggesting that relational aggression plays an important role in the development of that disorder as well (Natsuaki, Cicchetti, & Rogosch, 2009). Furthermore, those adolescents were also rated as likely to initiate fights, unlikely to be leaders, and likely to be viewed as uncooperative by their peers.

On the other hand, being a victim of peer bullying via both relational and physical aggression in childhood appears to increase risk for the development of borderline PD symptoms (Wolke, Schreier, Zanarini, & Winsper, 2012). Peer victimization (via relational and physical aggression, verbal aggression, and aggression against property) is also a risk factor for the development of schizotypal personality characteristics in schoolchildren between 8 and 16 (Fung & Raine, 2012). In the case of schizotypal personality, the relationship between peer victimization and the increased risk of schizotypal personality was mediated by increased social anxiety, paranoid ideation, and a dearth of close friends. Together, these findings suggest that relational aggression might be an important future research direction in furthering our understanding of the development of a variety of PDs.

As is evident from our previous discussion, interpersonal problems play an important role in the early development of many types of PDs. In fact, a lack of meaningful interpersonal relationships is a feature cutting across the many types of PDs. For example, a lack of close friends or being described as loners are some of the most common early schizophrenia spectrum (Cluster A)

symptoms (Carlson & Fish, 2005; Wolff, 1991). Furthermore, schizotypal traits in adolescents have been associated with deficits in social functioning, including hobbies, leisure activities, intellectual interests, and family relationships (Fonseca-Pedrero, Lemos-Giráldez, Paíno-Piñero, Villazón-García, & Muñiz, 2010). In contrast to children with Asperger disorder, a disorder which manifests commonalities in social impairment with Cluster A PDs (Cohen, Crawford, et al., 2005;Weston & Riolo, 2007), children with Cluster A PD symptoms might still feel the social isolation whereas children with Asperger Disorder feel indifferent about social interactions (Carlson & Fish, 2005).

In the case of Cluster B disorders, interpersonal maladaptation (such as interpersonal instability) has been conceptualized as a defining feature of borderline PD (Becker et al., 2006; Reich & Zanarini, 2001). Mothers have reported that their daughters with borderline PD began experiencing interpersonal problems in toddlerhood and childhood (Goodman et al., 2010). Interpersonal problems also appear to play an important role in the severity of borderline PD symptoms. Specifically, among adolescents with borderline PD, unstable interpersonal relationships were uniquely associated with nonsuicidal self-injury and suicide (Muehlenkamp, Ertelt, Miller, & Claes, 2011). This link was also found in a sample of Chinese adolescents, such that disturbances in interpersonal relationships were predictive of nonsuicidal self-injury (You, Leung, Lai, & Fu, 2012).

Finally, in the case of Cluster C PDs, adults with avoidant PD retrospectively reported less popularity in childhood and adolescence, having fewer meaningful relationships with adults, and less involvement in hobbies and athletics than did adults with no or other PDs (Rettew et al., 2003). Interestingly, they also reported that their caregivers showed more impaired social skills than did adults with other PDs. Taken together, these findings underline the defining role that interpersonal difficulties play in the development of multiple PDs even from a very young age.

Interpersonal Relationships: Later Life

Research suggests that as adults age, they prune their social networks, systematically removing negative or unimportant social contacts and strengthening their positive or important relationships (e.g., Carstensen, 1992). As a result, adults tend to have progressively smaller, but more meaningful social networks. This finding is consistent with the theory of selective optimization with compensation, a theory of adaption which states that as individuals age, they increasingly focus their attention on areas of high priority (selection) that offer meaningful benefits (optimization), while finding new ways to cope with aging-related losses and to maintain functionality (compensation; Baltes & Baltes, 1990). Specifically, the pruning of social relationships represents one instance of how individuals selectively optimize their meaningful relationships and cut their losses with their unimportant relationships.

Although we are unaware of any large-scale studies which specifically analyzed the relationships of older adults with PDs, informed speculation from various sources is possible. For example, in a case study of an older adult with narcissistic PD, the participant had drastically changing social networks from one time point to the next (Balsis et al., 2010). Individuals who she rated as being in her innermost circle at one point were later not reported at all or were relegated to a lesser circle. As this example suggests, individuals with PDs likely have marked impairment in the interpersonal realm, which would lead to fewer functional relationships as they age (e.g., because of burned bridges or avoidance of close relationships). Further, for the healthy individuals who are in the process of trimming their social networks as they age, individuals with PDs are likely candidates to be pruned because of their potentially difficult interpersonal style.

Relationships are also important because they provide a network of social support that can offer important services. Relationships provide the emotional and instrumental support that, while important for all individuals, may be especially important for older adults because of their increased dependence. Due in part to declines in their physical capabilities, older adults may need instrumental support for tasks that were once routine, such as driving, grocery shopping, personal hygiene care, and housecleaning. Without a system of social support, older individuals would also lack emotional support during potentially difficult transitions, such as the empty nest, retirement, and the deaths of one's parents and peers. In short, disrupted relationships due to PDs might leave one isolated during a time of increased need for social support. Rather than have a rich, supportive network of individuals on which one could rely, individuals with PDs may have to face the challenges of later life alone.

Identity: Early Life

Finally, the fourth component that plays an important role in the early development of PDs is identity disturbance (Fonagy & Bateman, 2008). Identity disturbances can be described as self-conceptualizations that are extreme, inflexible, and change unpredictably. For example, rather

than thinking about themselves and others in a nuanced way, individuals with identity disturbances might think of themselves and others as being all good or all bad (Tackett et al., 2009). Identity disturbances have also been conceptualized as made up of different factors, such as (1) lack of normative commitment—the difficulty in committing to stable values and perspectives about the future, (2) role absorption—the tendency to identify with a single role, which can change dramatically across time and situations, (3) painful incoherence—experiences of distress about feeling incoherent, and (4) lack of consistency—tendency to lack consistency in behavior and sense of self over time, all of which have emerged in both adult and adolescent samples (Westen, Betan, & Defife, 2011). This multidimensional identity disturbance construct has been associated with numerous PDs, but especially with borderline PD.

Distorted mental images about the self are one of the defining distinctions between normal personality traits and PDs (Tackett et al., 2009). Specifically, distortions in the cognitive perspectives of the self prevent people with PDs from adapting successfully to the social world that we live in, thereby influencing the interpersonal component of PDs. For example, identity disturbances can be associated with maladaptive interpersonal relationships given that, with an extreme and inflexible self-image, it is difficult for a person to successfully negotiate relationships with others. Similarly, identity disturbances can be associated with impaired emotion regulation, given that self-images that change unpredictably from a positive extreme to a negative extreme increase the likelihood for similarly extreme changes in emotions, thereby influencing risk for the emotional component of PDs. Furthermore, when adopting an extremely negative view of themselves that is inferior to others, individuals with PDs might rely excessively on others to bolster their self-esteem. A disrupted sense of self has been identified as one of five indicators in childhood that reflects the unsuccessful negotiation of developmental tasks (Geiger & Crick, 2001). Particularly in adolescence, consolidating one's identity is an extremely salient developmental task (Crawford et al., 2004).

In terms of the development of PDs, Shiner (2009) has described two maladaptive pathways in the normal development of identity that might be particularly relevant. Specifically, the first pathway involves difficulties with constructing a coherent life narrative, whereas the second pathway involves difficulties with integrating negative experiences into one's narrative. Adolescents on the first maladaptive pathway might have problems committing to a single coherent and integrated life narrative. They might also experience challenges in remembering distinct past events and instead concentrate on general and vague memories. Both problems can put those adolescents at risk for maladaptive psychological functioning. Adolescents on the second maladaptive pathway, on the other hand, might have specific weaknesses in employing adaptive ways of integrating negative experiences into their narrative, for example through coping strategies such as using positive explanatory frameworks (Pals, 2006). Furthermore, these adolescents might engage in maladaptive behavior such as incorporating a negative experience in such a way that it spoils a preceding positive experience, also called a contamination sequence (McAdams, 2009). Finally, these adolescents might struggle with meaning-making, i.e., creating positive meaning out of a negative event (McLean & Pasupathi, 2012). Taken together, a lack of adaptive coping strategies and use of maladaptive behaviors can have negative psychological consequences for youth identity development.

Identity disturbances are particularly relevant to Cluster B PDs that are associated with diffusion or fragmentation of identities (Fonagy & Bateman, 2008). Therefore, we focus here on summarizing findings for Cluster B PDs, such as borderline PDs, psychopathy, and narcissism. Of the Cluster B PDs, borderline PD has been most strongly linked with identity disturbances. Even in early childhood, children of mothers with borderline PD have self-representations that are more incongruent and shameful than those of their peers who have mothers without borderline PD, and these disturbances in self-representation have been related to maternal self-harm (Macfie & Swan, 2009). Furthermore, within borderline PD, the symptom of confusion about self appears to differentiate between nonsuicidal and suicidal self-injury (Muehlenkamp et al., 2011). This relationship between identity disturbances and nonsuicidal self-injury does not seem to be specific to borderline PD, either. Specifically, in late adolescence, self-esteem may partially to fully mediate the relationship between nonsuicidal self-injury and several PDs, including borderline, antisocial, dependent, depressive, avoidant, and negativistic PDs (Cawood & Huprich, 2011).

Among other Cluster B PDs, both psychopathy and narcissistic PD have been linked with identity disturbances. For example, self-serving cognitive distortions interact with psychopathic traits to predict antisocial behavior in adolescent boys and girls (Chabrol et al., 2011). Specifically, self-serving cognitive distortions predicted antisocial behavior only in adolescents who scored high on psychopathy. Furthermore, in early adolescence,

narcissism is related to an inflated view of the self (Bukowkski, Schwartzman, Santo, Bagwell, & Adams, 2009). In summary, identity disturbances play an important role in the development of a range of PDs, especially Cluster B PDs, and predict important outcomes of youth PD such as nonsuicidal or suicidal self-injury. These findings highlight the need for further research on the role that identity disturbances play in the full range of PDs, and the need to understand how pathways might be altered toward a more successful negotiation of the developmental task of identity consolidation.

A concept that is highly relevant for identity development is that of personal narratives, or life stories (McAdams & Pals, 2006; McLean & Pasupathi, 2012). Life narratives are especially critical during the developmental period of adolescence, when youth become more competent to narrate their complex life story coherently (Habermas & de Silveira, 2008; Shiner, 2010). The creation of adolescents' personal narratives is deeply rooted in their social context (McLean & Pasupathi, 2012; Shiner, 2009). For example, from an early age, children begin constructing their stories with the help of other adults, usually their caregivers, which then affects their narrative complexity (e.g., Fivush, Haden, & Reese, 2006). Later in adolescence, the youth's peer group is the most important social context that actively shapes their stories. Therefore, given the importance of interpersonal relationships in the development of PDs, it becomes clear that personal narratives hold special relevance for the development of these disorders, as well. Although previous editions of the *DSM* have considered identity disturbances particularly important in their conceptualization of BPD, the field now recognizes such disturbances as important in the conceptualization of many PDs. Therefore, additional attention to the development and assessment of life narratives will be especially relevant for the study of youth PDs.

Identity: Later Life

Less is known about the process of identity formation in later life, let alone the pathological aspects of identity in later life. Erikson's (1950) influential model of sequential developmental conflicts offers the perspective that individuals are tasked with the process of identity formation during adolescence, but the development and maintenance of identity is surely a life-long process. There is evidence suggesting that individuals' narrative identities become more complex and sophisticated with age (see McAdams & Olson, 2010). In older adulthood, a shift may occur from developing one's identity to reflecting on one's identity (Waterman & Archer, 1990). Consistent with Erikson's (1950) stage of ego integrity versus despair and the life review (Butler, 1963), older adults may begin to reminisce and reanalyze their lives.

Rather than approach late life with integrity as Erikson (1950) envisioned the healthy person to do, individuals with PDs may react to later life with despair over a life fraught with negative affect, disrupted social relationships, and a potentially unclear sense of self. However, for individuals who have successfully internalized (or defended) their personality pathology, they may die how they lived. That is, for a severe narcissist, for example, he or she might die believing in the delusions of grandeur that supported his or her ego throughout life. But for individuals who are aware or who become aware of how their life is lacking, later life could be a difficult period, indeed; one fraught with sadness and regret over what could have otherwise been. We now turn to critical developmental periods for PDs across the life span.

CRITICAL DEVELOPMENTAL PERIODS FOR PDs

Given recent support for both stability and change in PDs over time (Tyrer, 2005), identifying critical developmental periods in the development of PDs might help elucidate periods of life when PDs are most conducive to intervention and prevention. Identifying such periods requires attention to both normal and abnormal developmental processes to identify maladaptive changes that deviate from the norm (Tackett, et al., 2009). We will focus our discussion on four critical developmental periods that appear to be important for the development of personality pathology. Specifically, we focus on early life (including infancy and early childhood), the transition from middle childhood to early adolescence, the transition from late adolescence to early adulthood, and the period of later life.

Infancy–Toddlerhood

Despite current *DSM* conceptualizations of PDs as having an adult onset (Crawford, Cohen, & Brook, 2001a), historically, PD characteristics have been conceptualized as originating early in life (Paris, 2003; Tyrer, 2007). Factors such as hostile parents, disorganized attachment styles, and temperament in early childhood have been related to PD symptoms in adulthood, with borderline PD symptoms receiving the most research attention (Carlson et al., 2009). We review these constructs in more detail and briefly review biological findings as well.

As previously discussed, one construct that is critical for the development of PDs in early life is attachment (Crawford et al., 2006; Raine, 2006; Weston & Riolo, 2007). Specifically, disrupted attachment with a caregiver during early life sets a pattern for disrupted interpersonal relationships in later life (Sroufe, Carlson, Levy, & Egeland, 1999) whereas beneficial parenting behaviors might be a protective factor against the development of maladaptive personality traits (Johnson, Liu, & Cohen, 2011). The infant years from birth until age 2 have been identified as particularly critical for the formation of attachment. For example, for children characterized by an angry temperament, prolonged separation from their mother predicted later schizotypal PD symptoms, but only if the separation took place during infancy and not later in childhood (Anglin, Cohen, & Chen, 2008).

As previously discussed, the development of borderline BD has been most closely linked to attachment theory (see Bradley & Westen, 2005; Levy, 2005). For example, although the findings have been mixed, separation from parents during the early years has also been associated with borderline PD development (Levy, 2005; Reich & Zanarini, 2001). A number of research findings speak to this. Children with borderline PD symptoms were more likely to have mothers who exhibited disrupted communication patterns (Levy, 2005). Adolescent girls with borderline PD were more likely to have had disrupted attachment than did adolescent girls with other mental health problems (Ludolph, Westen, Misle, & Jackson, 1990). Furthermore, increases in borderline PD symptoms from early adolescence to middle adulthood have been associated with maternal separation in early childhood (Crawford et al., 2009). For men, separation from caregivers in early childhood, especially before the age of 5, has been associated with a range of Cluster B PDs (not only borderline PD; Lahti et al., 2012). Given that interpersonal relationships are at the core of both attachment theory and PD conceptualizations, it is not surprising that the early years can leave a lasting impact on the development of PDs (Crick et al., 2005).

More extreme parental neglect during the childhood years has also been implicated in the development of a range of PDs. For example, maltreatment in the form of both emotional and sexual abuse during childhood has been associated with borderline PD in adulthood, at least in women, (Hernandez, Arntz, Gaviria, Labad, & Gutiérrez-Zotes, 2012), hyperbolic temperament, which is thought to underlie borderline pathology (Hopwood & Zanarini, 2012), and general personality pathology in incarcerated adolescent boys (Nederlof, Van der Ham, Dingemans, & Oel, 2010). A study conducted in a Chinese sample found childhood abuse to be more prevalent in patients with borderline PD than in patients with other Axis II or Axis I disorders (Huang et al., 2012).

Another construct that is critical for the development of PDs in early life is emotion- and self-regulation (Crick et al., 2005). For example, early disrupted attachment may deprive the child of opportunities to develop adaptive emotion regulation, which then increases their likelihood to develop borderline PD (Fonagy & Bateman, 2008). In contrast, dysregulated temperament—characterized by high stress reactivity—may increase a child's likelihood for disrupted attachment with their caregiver, which, in combination, increases the child's likelihood to develop borderline PD (Gunderson & Lyons-Ruth, 2008). Furthermore, the child's temperament may interact with the caregiver's temperament in increasing negative parenting, which then interferes with the development of adaptive emotion regulation and interpersonal relationships (Gunderson & Lyons-Ruth, 2008; Levy, 2005). Adult individuals with borderline PD retrospectively reported more difficulties with emotion regulation during childhood than did individuals with other PDs (Reich & Zanarini, 2001).

Other individual factors in infancy–toddlerhood may also increase risk for later PDs. Increased emotional and behavioral problems, impulsivity, and decreased cognitive functioning in early childhood have also been associated with borderline personality features in middle childhood (Belsky et al., 2012). Maternal reports of moodiness in infancy differentiate adults with borderline PD from their siblings without the disorder (Goodman et al., 2010). In addition, fearful emotions also seem to play an important role in the development of some PDs, such that increasing withdrawal has been identified as a possible early predictor of avoidant PD (Eggum et al., 2009) whereas low fearfulness in early childhood has been associated with psychopathy characteristics (Glenn et al., 2007). Together, these findings underline the importance of a range of individual differences during the early years for the development of PDs.

In addition to disrupted attachment and individual difference factors, stress and trauma during early life have effects on the development of PDs. Such effects may be mediated by functional and structural brain abnormalities (Raine, 2006; Skodol et al., 2002). For example, asphyxia, delivery complications, and prematurity have all been associated with PDs in a forensic population, suggesting that abnormal brain development might underlie those disorders (Fazel et al., 2012). Other early biological indicators, such as body growth, have also been associated

with the development of PDs. For example, low weight at age 6 months and 11 years was associated with later PDs in men in one study (Lahti et al., 2011). Another study found that longer skin-conductance half-recovery times to negative stimuli in early childhood were associated with higher psychopathy scores in adulthood (Glenn et al., 2007). Together, these findings suggest that certain biological factors in the early years may also predispose youth to the development of multiple PDs later in adulthood.

Middle Childhood–Early Adolescence

By early adolescence, the stability of PD symptoms begins to reach levels comparable to those in adulthood (Bukowski et al., 2009; Cohen, Crawford et al., 2005; Johnson et al., 2000; Raine, 2006; Salekin et al., 2008), highlighting this as another potential critical period for PD development. In fact, across adolescence, Cluster B PD symptoms were found to show greater stability than even internalizing or externalizing symptoms (Crawford et al., 2001a). The stability of Cluster B personality traits appears to be highly heritable (Bornovalova et al., 2009; Forsman, Lichtenstein, Andershed, & Larsson, 2008). Furthermore, the association between psychopathic personality in adolescence and antisocial behavior in adulthood appears to be mediated by genetic factors (Forsman, Lichtenstein, Andershed, & Larsson, 2010). Among Cluster A symptoms, paranoid PD symptoms showed the greatest stability between the ages of 13 to 16 (Cohen, Crawford, et al., 2005). Although PD symptoms reach adult-levels of stability by early adolescence, important differences still exist in their manifestation. For example, Speranza et al. (2012) found that affective stability was particularly central to BPD in adolescence, which is not necessarily the case later on in life. Zanarini and colleagues (2011) found that BPD in childhood was more characterized by anger and moodiness than in adulthood, whereas BPD in adulthood was more characterized by impulsivity, identity disturbances, and paranoia. In addition, in the case of schizotypal traits, Fonseca-Pedrero and colleagues (2012) found that younger adolescents were characterized by lower scores in social anxiety and disorganization and higher scores in odd thinking, language, and lack of friends compared with older adolescents.

Multiple domains highly relevant to adolescents appear to play a critical role in the development of PD symptoms: Identity consolidation, peer relationships, and socio-economic factors and risky behaviors. During adolescence, identity consolidation is one of the most important tasks (Crawford et al., 2004), as previously described in this chapter. In the case of narcissistic traits specifically, preadolescence has been identified as a critical period to measure the development of such traits given that more normative exaggeration of self-competence decreases around age 10 years (Thomaes, Bushman, Stegge, & Olthof, 2008) and by early adolescence, narcissistic traits have been associated with an inflated self-view (Bukowski et al., 2009). The same period has also been identified as critical for interventions given the greater malleability of children's self-views during preadolescence than during late adolescence (Thomaes, Bushman, et al., 2008; Washburn, MacMahon, King, Reinecke, & Silver, 2004).

In addition to the task of identity consolidation, navigating social relationships is an important developmental task that can introduce normative stress during early adolescence. In the case of narcissistic traits, the possible increase in shame from childhood to adolescence due to youth's greater self-consciousness could moderate the effect of narcissistic traits to predict aggressive behavior, such that children high in narcissistic traits are likely to aggress only if they feel ashamed (Thomaes, Bushman, et al., 2008). Narcissistic traits in early adolescence have been associated with reactive and relational aggression as well as a diminished stress response (Bukowski et al., 2009). Poor peer relations have been linked to PD symptoms in middle childhood–early adolescence across a range of PD domains (Fung & Raine, 2012; Natsuaki, Cicchetti, & Rogosch, 2009; Wolke et al., 2012). Furthermore, an absence of meaningful relationships in childhood may play a cascading role in the development of schizoid PD (Lenzenweger, 2010). Physical and social aggression in middle childhood predicts adolescent borderline and narcissistic features in adolescence (Goodman et al., 2010; Underwood et al., 2011). Taken together, these findings suggest that disrupted interpersonal peer relationships, especially those characterized by aggression, likely have both a moderating as well as a direct effect on the development and maintenance of PDs during this developmental period, as the salience of the peer group increases.

The greater social environment that youth spend most of their time in, namely schools, has also been found to have a profound impact on the development of PD symptoms. Specifically, schools with climates high in learning focus and student autonomy were associated with decreases in Cluster B and A symptoms, respectively (Kasen, Cohen, Chen, Johnson, & Crawford, 2009). In contrast, schools with climates high in conflicts or informality among students and teachers were associated with increases in Cluster A and C symptoms, underlining both

the positive and negative influences of school climates on youth PD symptoms. Communication more generally becomes increasingly important during middle childhood. For example, communication patterns show a significant decrease in loose associations and illogical thinking after age 7, suggesting that prior to middle childhood, these communication styles are more normative. Consequently, middle childhood has been implicated as a critical developmental period for the disrupted communication that characterizes schizotypal PD (Caplan, 1994). Furthermore, theory of mind deficits have also been associated with positive schizotypy symptoms in adolescents (Barragan, Laurens, Navarro, & Obiols, 2011). In summary, both the social environments of peers and of schools have been shown to have a strong influence on the development of a range of PDs during the early adolescent period. In addition, in the case of Cluster PDs, communication that is necessary for adaptive functioning in any of the social environments is especially crucial and may become more impaired by middle childhood.

In the case of antisocial PD, the timing of conduct disorder symptoms has been implicated as especially important. Specifically, early onset of severe conduct disorder may increase the likelihood for later development of antisocial PD (Moffitt, Caspi, Harrington, & Milne, 2002; Paris, 2008). This prediction of Axis I disorders to antisocial PD seems to be unique to conduct problems and does not generalize to internalizing or substance use problems in adolescence (Diamantopoulou, Verhulst, & van der Ende, 2010). Furthermore, this unique association between conduct disorder and antisocial PD may be at least partially mediated by early-onset alcohol abuse (Khalifa, Duggan, Howard, & Lumsden, 2012). In fact, some researchers have argued that stable conduct disorder during childhood might be categorized as a PD (Cohen, Crawford, et al., 2005). Furthermore, violent conduct disorder symptoms increase youth's risk for the development of antisocial PD (Gelhorn, Sakai, Price, & Crowley, 2007) and adults with antisocial PD who have a history of conduct disorder have been found to be more antisocial than have adults without such a history (Walters & Knight, 2010). Thus, antisocial PD often appears to originate with early onset and severe conduct problems, including alcohol use and violence, and these early problems seem to have a lasting and worsening effect on the presentation of antisocial PD.

Early antisocial behavior may result in multiple outcomes, however, such that individuals who stay on the path of antisociality can be differentiated from those who change to a path of avoidance and social isolation (Rutter et al., 2006). In addition, these paths may vary by gender. One study found that only girls who showed disruptive behavior symptoms in midadolescence exhibited Cluster B symptoms by early adulthood (Crawford, Cohen, & Brook, 2001b). Furthermore, (incarcerated) girls might show a unique relationship between adolescent attention deficit hyperactivity disorder and psychopathy that boys do not show (Sevecke, Kosson, & Krischer, 2009). Specifically, Sevecke and colleagues found that the relationship between attention deficit hyperactivity disorder and psychopathy in boys was explained mostly by the association between attention-deficit/hyperactivity disorder and conduct disorder, whereas the relationship in girls explained unique variance over and above conduct disorder. These multifinality effects across gender are particularly interesting given the low prevalence of antisocial behavior in adult women (Guzder et al., 1996). In contrast, attention deficit hyperactivity disorder and oppositional defiant disorder symptoms prospectively predicted borderline PD symptoms in a clinical sample of adult men (Burke & Stepp, 2012) as well as a sample of adolescent girls (Stepp, Burke, Hipwell, & Loeber, 2011). Overall then, these findings suggest that gender is an especially crucial moderating factor in the development of antisocial PD during adolescence that requires further study to fully understand the developmental path of the disorder.

Socioeconomic factors have also been implicated in the development of antisocial behavior in adolescence. Specifically, although these risk factors might not influence the emergence of psychopathic traits, they might nevertheless motivate children characterized by psychopathic traits to utilize more antisocial strategies to achieve their goals (Blair et al., 2006). However, one empirical study found that the development of psychopathic traits from early adolescence to early adulthood in boys was influenced by low socioeconomic status, a delinquent peer group, and the experience of corporal punishment (Lynam, Loeber, & Stouthamer-Loeber, 2008). In addition, one study found the association between psychopathic traits and risky decision-making in preadolescence to be moderated by the child's social class, such that the association was significant only for children from high social classes (Gao, Baker, Raine, Wu, & Bezdjian, 2009). So far, the exact influence of socioeconomic factors on the development of psychopathic traits is unclear. Specifically, future studies are needed to further clarify whether socio-economic factors have a direct or moderating effect (or both) on the development of these maladaptive traits.

Finally, given the increase of general risk taking during adolescence, it is not surprising that risk taking behaviors

have also been found to have an important effect on the development of PDs. Sensation seeking in childhood has also been related to borderline PD, potentially explaining the increased risk of sexually transmitted diseases and other health issues that have been associated with the disorder (Chanen et al., 2007). Other risky behaviors such as early substance abuse have also been implicated in the development of PD symptoms. For example, early cannabis use in adolescence has been found to predict schizotypal PD symptoms in middle adulthood over and above other risk factors such as adolescent schizotypal PD symptoms or comorbid Axis I disorders, suggesting that the mechanism regarding this link are an important future research direction (Anglin et al., 2012) whereas early-onset alcohol abuse has been found to mediate the link between early conduct disorder and later antisociality in incarcerated males (Khalifa et al., 2012). Overall, these findings again suggest that risk-taking behaviors may be related to the development of a range of PDs in multiple ways (e.g., directly, as a moderator, or as a mediator), underlining the importance of further study on the topic.

Late Adolescence–Early Adulthood

The transition to adulthood is another potential critical period in the development of PDs for several reasons. During this period, people with personality pathology tend to increasingly deviate from the norm (for a review, see Clark, 2005) and life quality of individuals with personality pathology during this transition is similarly low to that of adults with the same pathology (Feenstra et al., 2012). Furthermore, borderline PD traits increase in their heritability from adolescence to adulthood (Bornovalova et al., 2009), which may reflect a loosening of environmental constraints on borderline symptomatology during this developmental transition. Whereas the co-occurrence between borderline PD traits and substance use is primarily due to shared environmental factors in adolescence, it is increasingly due to genetic factors in early adulthood (Bornovalova et al., 2012), again suggesting a developmental shift in the relative impact of environmental influences. In the case of psychopathic traits, both affective-interpersonal features and social deviance have been found to be similarly heritable at age 17 and genetic factors seemed to mediate the association between social deviance and environmental risk factors (Hicks, Carlson, Blonigen, Patrick, Iacono, & McGue, 2012).

One of the most important developmental tasks during this period is becoming an independent adult outside of the home of one's family of origin, which can be impeded by the maladaptive interpersonal patterns associated with PDs (Cohen, Chen, et al., 2005; Johnson, Chen, & Cohen, 2004). Another important developmental task in this period is developing one's own intimate relationships, which may also be impeded by certain PDs. For example, for girls, the negative association between intimacy and Cluster B PD symptoms is stronger in late than in early adolescence (Crawford et al., 2004), suggesting that—as intimate relationships become the focus of developmental tasks—they also start to have a stronger effect on Cluster B characteristics.

Among individuals with PD characteristics, those with high levels of Cluster A PD symptoms in adolescence show the greatest impairment during the transition to young adulthood (Cohen, Crawford, et al., 2005). This pattern fits well with the rising prevalence of severe psychosis during early adulthood. An example of deviation from social norms is that individuals with Cluster A PDs are more likely to be early parents during this developmental period (Cohen, Chen, et al., 2005). Heavy use of cannabis during this transition, but not later in adulthood, appears to predict schizophrenia diagnoses later in life (Rutter et al., 2006), suggesting that this might be a critical developmental period for the brain during which it is particularly susceptible to the heavy use of drugs. Findings regarding other PD characteristics further support the role of neurodevelopmental factors during this transitional period. For example, in the case of borderline PD, neurological abnormalities (i.e., reduced volume in the anterior cingulate gyrus) appear as early as adolescence (Goodman et al., 2011) as they do in adulthood (Hazlett et al., 2005; Tebartz van Elst et al., 2003). In the case of schizotypal symptoms, interpersonal symptoms were associated with executive functioning deficits, fine motor dyscoordination, and some physical anomalies in adolescence and, for a smaller subsample of these individuals, these neurodevelopmental factors were already present in middle childhood (Hans et al., 2009). Taken together, these findings suggest that genetic and neurophysiological factors may be present by adolescence and affect PD development during the transition to adulthood.

Later Adulthood

Later adulthood is also a critical time to measure PDs and associated outcomes. Do PDs develop for the first time in later adulthood? This is an important question that, when analyzed carefully, reveals fundamental issues about PDs that remain to be addressed. PDs, by their very definitions,

are of a long duration, and can be traced back to early adolescence. By this definition, it would seem unlikely that a person would enter later life and then develop a PD. Yet there is evidence that PDs can emerge in later adulthood or become functionally problematic for the first time in later adulthood (see Oltmanns & Balsis, 2011). Here we return to the two fundamental PD measurement problems mentioned at the outset—the arbitrariness of diagnostic thresholds and the categorical approach to measuring PDs.

How can we understand the development of a PD in late life? To do so, it is helpful to again consider the issue of thresholds and the somewhat arbitrary marking of them. Likely, there is not something qualitatively different between a person who meets four items verses five items of the borderline PD diagnostic set, for example. Both people are potentially having problems in their lives. Why the threshold for this PD was set at five items to meet diagnosis is not entirely reasoned. Indeed, a handful of the makers of *DSM* have indicated that the thresholds are at least somewhat arbitrary (Oldham, 2007). Given the somewhat arbitrary nature of the PD thresholds, it becomes easy to imagine a person who has subthreshold levels of a particular PD at time 1 who later rises above threshold due to some stressor. Consider a person who at the age of 20 met 4 of the 8 criteria for histrionic PD. Imagine that the person meets the same number of criteria at age 40 and 60. But, then, imagine that this person at the age of 65 experiences the death of her husband, who acted as an influence on dampening some of her natural tendencies for eroticization. Upon his death and the end of his influence, she may become especially exhibitionistic, for example, and now meets 5 of the 8 criteria, thus qualifying her for a diagnosis. From a distance, the data would appear as though the PD had emerged in later adulthood for the first time. However, as this example suggests, the apparent emergence of the PD at the age of 65 could result in part because the threshold system that is currently used is somewhat arbitrary and there is little difference between someone who meets four versus five criteria. In this example, the latent PD propensity was always present and was revealed when the woman's husband died. In this way, later life brings with it many contextual changes, like the death of a spouse, that present problems for our measurement systems. But these contextual changes can also be seen in another light. These later life changes can be the very things that allow for the emergence of an officially diagnosable PD.

Another critical context change that occurs around later life that might lead to the emergence of latent PD pathology is retirement. Retirement can lead to a major role change, financial change, as well as a challenge to one's identity. For certain individuals, such as a younger man with latent narcissistic PD, a career can fulfill many of their narcissistic needs (e.g., the need for power, ego confirmation) through socially acceptable means, such as occupational successes. When older, and without these types of career outlets and reinforcers, this older adult might resort to seeking reinforcement through other means, perhaps by denigrating others within the confines of his small social circle. So what was just below threshold, and may be socially enabling at a younger age, could become social disabling in later life. Here again, the disorder might be diagnosed for the first time in later life.

One can easily imagine other major critical periods in later life that could give rise to PD onset. For example, in late life, a person's health often begins to change. A younger person with a certain amount of paranoia might not show functional impairment associated with paranoid PD because he has a healthy body and reasons that he can engage in certain degrees of self-protection in public if needed, as described previously in this chapter. That same individual, now old, frail, and vulnerable, might find himself trapped in his home, still paranoid about others but now afraid to leave the house. In this example, the PD might interact with changes in health to cross some threshold of dysfunction for the first time in later life.

The bottom line is that later life is a dynamic time with lots of changes that can give rise to previously unseen PD pathology. The extent to which these late life changes reveal PD pathology is not well understood because we do not currently have good data upon which to base such observations. Clearly, though, examining PD pathology in later life would allow us to understand the stability and changeability of PD pathology across the life span and help us to understand how context affects the presentation of PD pathology even into later life.

CONCLUSIONS AND FUTURE DIRECTIONS

The current chapter had multiple goals, with one overarching theme: a desire to understand PD development across the life span within a developmental psychopathology framework. PDs lend themselves especially well to a developmental psychopathology perspective, as the rich and growing literature on normal-range personality measurement and development has much to offer a better understanding of measurement and development of personality pathology. We reviewed literature on the

longitudinal course for both normal and pathological personality, which show numerous similarities to one another. Importantly, such studies point to converging evidence for both stability and change in the development of normal and abnormal personality across the life span. Such evidence supports the need to examine the emergence and impact of PDs in early life, while also emphasizing their potential for change and the need to better understand the moderating roles of context and developmental stage.

Although we largely confined ourselves to language codified in the *DSM-IV* and *DSM-5* approach to PD conceptualization (which are virtually identical), we organized the literature using a different framework. Specifically, we examined core, cross-cutting components for PDs (traits, emotions, relationships, and identity), as well as critical developmental periods for PDs (infancy–toddlerhood, middle childhood–early adolescence, later adolescence–early adulthood, and later adulthood) to organize the empirical literature reviewed here. The decisions to explore common underlying components within a developmental context are resonant with a developmental psychopathology perspective as well. This approach speaks more directly to etiology, developmental pathways, multiple levels of analysis, and potential targets for intervention than would a strictly diagnostic framework. As a result, we hope that the information contained in the current chapter will apply more broadly across various types of personality pathology and will extend to other forms of mental disorder and other potential developmental outcomes. Personality is surely connected with virtually any form of psychopathology, thus holds much greater import than a disorder-specific perspective would convey.

Translational Implications

There are a number of translational implications that follow from the present chapter. In particular, the organization of the current chapter focused on cross-cutting components for PDs (traits, emotions, relationships, and identity) and critical developmental periods for PDs (infancy–toddlerhood, middle childhood/early adolescence, later adolescence/early adulthood, and later adulthood) both of which point to potential targets for intervention and prevention. Cross-cutting, core components of PDs are consistent with the developmental psychopathology emphasis on multiple levels of analysis, and further offer highly relevant targets for preventive interventions. Research suggesting that personality trait change is more likely to lead to PD change than the reverse (Warner et al., 2004), for example, suggests that core traits may be a more meaningful and effective target of intervention than PDs themselves. Increasing research is pointing to evidence for systematic personality change across the life span, which further highlights the translational value of core components of PDs, such as personality traits. Indeed, youth traits have already shown early success as targets for preventive interventions of early PD (Chanen et al., 2008).

Similarly, a better understanding of critical developmental periods point to sensitive periods in the development of personality pathology that may also be highly amenable to preventive intervention efforts. Importantly, critical developmental periods for PD development emerge well before PDs are typically diagnosed in late adolescence or adulthood. Thus, it is critical that educators, researchers, parents, and clinicians, begin attending to core components of PDs long before the potential emergence of full-blown personality pathology. Adaptive development of early attachment, constructive emotion regulation skills, and productive interpersonal relationships may all be critical to developmental success, including decreased risk for later personality pathology. Such developmental milestones can be nurtured prior to those developmental periods in which they are most salient. In addition, children identified as higher risk based on such developmental milestones may represent key targets for preventive interventions, particularly if deficits in core components of personality pathology (e.g., the presence of high-risk personality traits) are also identified.

In addition, there are major impediments to understanding how PDs present themselves in early and in later life because the current measurement tools simply don't work as well for children, adolescents, and older adults as they do for younger adults (who generally reflect the dominant population in research and practice). Developing accurate measures to assess personality and personality pathology in children, adolescents, and older adults is of great practical importance. Once accurate measures are available, clinicians will be able to better identify and treat these populations with PDs, and thereby enhance the well-being of both younger and older people, and their families.

Future Directions

The future is bright for an increasingly nuanced perspective on personality pathology across the life span. As this chapter highlights, however, there is much work to be done. Optimism comes from recent advances in child personality and PD research, which suggest a growing interest in measuring and investigating personality pathology in early

life. It will be essential for PD researchers interested in children and adolescents to take the existing measurement crisis seriously. Assessments based on those created for adults will remain critically valuable to advancing the field, yet they do not offer a comprehensive developmental perspective on early personality pathology. Further work examining those early PD constructs most relevant at different ages (which may or may not match those often studied in adults), developing empirically based bottom-up measurement tools, and examining issues of informant discrepancy and integration represent key contributions for the field to realize in coming years.

Furthermore, although our knowledge regarding PD stability and flexibility is steadily advancing, our understanding of the moderators and mediators of this stability and flexibility is still limited. Thus, we think that the moderating roles of context, including cultural, socioeconomic, and gender variations in contexts, need to be better understood. Identification of mechanisms behind the development of personality pathology across the life span will be especially important in advancing the translational implications of this research given that these mechanisms could present potential treatment targets. In addition, after reviewing the literature with a focus on critical developmental periods for PDs, it became clear that future studies need to focus on more circumscribed developmental periods to uncover factors that are relevant in one developmental period but not in another that would be missed if data were aggregated across developmental periods. Finally, more long-term studies at the extreme ends of development (early childhood and late adulthood) as well as on a range of PDs or personality pathology traits will also move the field forward in its quest to understand PD developmental across the life span to best help individuals at all stages of their life.

Additional future directions can be identified from a life span perspective of PD development. For example, personality and PDs need to be linked more clearly to the most important outcomes for older adults, such as disease and mortality. What role does personality play in causing these outcomes? To answer this question, it will be necessary to follow individuals longitudinally across the life span to examine how personality contributes to these important outcomes, which tend to occur in later life. In addition, research will need to show the differential impact of personality and PDs across the life span on other key variables. How do PDs disrupt natural social and emotional development in later life? And what are the consequences of this disruption for the individual with the PD, their intimate relationships, families, and the health care system? Later life is a unique time with unique challenges. Individuals are transitioning to retirement, facing diminishing health and vitality, changing roles from provider to dependent, and needing to lean on others for care and support. How exactly does personality and PDs affect these transitions and situations? These and other fundamental questions about personality and PDs can be answered by considering their consequences in later life. Finally, when we consider later life, we are required to reexamine basic theories and assumptions about PDs. We see that in later life, PDs can emerge for the first time, challenging the notion that PDs mellow with age. Across all of these questions and perspectives, it becomes clear that studying PDs within the context of personality traits might provide us with the best avenue for future improvement. And indeed, as articulated throughout this chapter, studying these important constructs in later life—when many important outcomes occur—will benefit PD research, help us reach more valid interpretations and understandings of these debilitating disorders, and ultimately help us discover effective ways to treat those affected by PDs.

Taken together, attention to developmental issues will likely represent important contributions to the broader field of PD theory and research in the coming years. Although studying younger and older ages than is the norm presents numerous challenges, such challenges must be embraced by the field. Doing so should lead us all to a better understanding of the phenomena we study and, ultimately, the best approaches to preventing and treating the problems that emerge.

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CHAPTER 24

Toward a Developmental Psychopathology of Personality Disturbance: A Neurobehavioral Dimensional Model Incorporating Genetic, Environmental, and Epigenetic Factors

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BACKGROUND AND CONTEXT FOR A DEVELOPMENTAL MODEL OF PERSONALITY DISTURBANCE

Personality disorders have long held the fascination of clinicians actively engaged in the diagnosis and treatment of psychopathology. For most of the past 100 years, the psychiatric, clinical psychological, and psychoanalytic perspectives have viewed personality disorders (PDs), which affect about 10% of the population (Lenzenweger, 2008), as (1) relatively enduring and trait-like disorders, (2) largely psychological in nature, (3) fixed firmly within the person over time, and (4) likely the result of dyshygienic childrearing practices. The primary models of the etiology of personality disturbance hailed largely from the psychoanalytic realm, had little connection to what was known empirically about normal personality or temperament, and contained virtually no representation of neurobiology processes or genetic influences with respect to etiology or development. Moreover, for much of last century the prevalence of personality pathology in the general population was essentially unknown (with guesstimates varying widely, even wildly), but clinicians caring for patients observed such pathology frequently in their patients. Finally, many clinicians and theoreticians pondered the possibility that certain personality disorders such as the psychopath or the borderline were *qualitatively* (a difference by kind or type, not degree) demarcated from the range of diversity seen for normal personality (Cleckley, 1964; Frosch, 1970; Hare, 1993; Kernberg, 1968; Rado, 1960; Reich, 1933/1949). Indeed, generations of clinicians and researchers have been taught that personality disorders (1) are relatively discrete entities that diverge from

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[1]Color versions of Figures 24.3, 24.6, 24.7 and 24.9 are available at http://onlinelibrary.wiley.com/book/10.1002/9781119125556

normal personality in an implicitly qualitative manner (not unlike the way a broken leg or viral infection demarcates a qualitatively different health status); (2) are to be regarded as minimally responsive to treatments; (3) set like plaster in terms of their longitudinal consistency across the life course; (4) are the result of unifactorial psychological processes (e.g., single traits, single process models, such as excessive aggression leads to personality pathology); (5) are relatively common in the population (as suggested in the *DSM* nomenclature since 1980); and (6) are often the result of poor parenting practices (e.g., severe discipline, childhood sexual abuse).

Scientific inquiry into the nature of personality disorders was relatively somnolent prior to 1980, with most energy directed toward theory (without concomitant empirical research) and clinical treatment issues. A sea change occurred with the advent of explicit diagnostic criteria for the personality disorders in the *DSM-III* (American Psychiatric Association, 1980). While the diagnostic criteria for personality disorders in the *DSM-III* were not formally operational as has been asserted by some, they were clearly articulated and provided a rubric for the identification of clinically significant deviations in personality functioning. Scientific inquiry into the definition, classification, and nature of personality disorders really began in earnest in the era ushered in by the *DSM-III*. By the mid-1980s the personality disorder research area found itself largely concerned with debates regarding the proper definition of PDs (e.g., categories vs. dimensions?) as well as the refinement and continued development of diagnostic instruments for the assessment of PDs. This was so because the PDs had only recently been defined explicitly (i.e., *DSM-III,* APA, 1980) and instrumentation for reliable assessment had only just begun to emerge (forerunners of the *IPDE*, *SCID-II*, and *SIDP*). At that time, there was also a growing scientific interest related to factors impacting the diagnosis of personality pathology, for example, (1) the comorbidity of PDs with Axis I disorders; (2) the challenging reality of multiple personality disorders in the same individual; (3) the utility of interview versus self-report assessment instruments (Zimmerman, 1994); and (4) possible sex/gender bias in the definition/diagnosis of PD's (see Lenzenweger & Clarkin, 2005, for review). Many of these issues continue to be of concern even today and were, indeed, taken up in the attempted revision of the personality disorders section of the recently published *DSM-5* (American Psychiatric Association, 2013).

Basic definitional and assessment issues were rightfully the focus of PD research in the 1980s. However, by the end of the 1980s, more substantive and methodological questions had begun to loom large for the PD research area. Many investigators began to seek answers to fundamental questions that lacked empirical illumination or adequate development, such as:

1. Does mental state impact the assessment of personality disorders, which are putatively more enduring (i.e., a state–trait issue)?
2. Could one develop a screening instrument for personality disorders that would be reasonably efficient (i.e., generate few false negative cases) for application in epidemiologic studies?
3. What is the epidemiology of personality disorders in *nonclinical* community populations?
4. Can one find *DSM*-defined personality disorders in other countries (cultures)?
5. Are there diagnostic approaches to personality disorders that might supplement traditional methods and incorporate information from observers other than clinicians?
6. What would a theory of PDs look like that incorporates contemporary neural science, affective neuroscience, genomics, temperament, personality, and so on?
7. What is the precise nature of the natural history and course of personality psychopathology when studied in longitudinal perspective?

PRIOR ATTEMPTS TO UNDERSTAND PERSONALITY DISORDER: LEXICAL TRAITS, HYBRID CONSTRUCTS, AND AXIS I DISORDERS EXTENDED

Our focus in this chapter is on the development of a model of personality disturbance that incorporates contemporary neural science, affective neuroscience, genomics, epigenetics, and personality. However, before presenting our perspective on this problem, it is important to briefly review other prior approaches seeking to link personality to pathology to either personality or Axis I psychopathology. In short, most other models connecting personality factors to personality disorder have argued that personality disorders represent (1) subsyndromal or preclinical extensions of Axis I disorder liabilities; (2) the result of the impact of moderating factors acting upon personality systems; or (3) simple noninteractive extremes of normally occurring personality dimensions (i.e., very low or very high values on a measured personality dimension). In discussing these models we illustrate the proposed

relevance to personality disorder specifically with illustrations based on borderline personality disorder. Let us consider the last of these possibilities first. Consider the popular five-factor (or BIG-5) approach to characterizing personality. It is an approach that hails from academic personality psychology efforts to distill personality dimensions from language-based trait descriptors and describes normal personality in terms of five continuous dimensions, namely, extraversion, neuroticism, openness, agreeableness, and conscientiousness (see Saulsman & Page, 2004; Widiger, 2005; and Widiger & Costa, 2012 for reviews). In the five-factor approach, PDs are viewed as reflecting simple extremes on naturally occurring normal personality dimensions, most often neuroticism or agreeableness. For example, in the five-factor approach, borderline personality disorder is associated principally with low levels on the agreeableness dimension. The empirical basis for linking the five-factor model of normal personality to personality disorder is to be found in correlational studies that have reported associations between the five-factors (typically measured with popular self-report inventories) and scores on the various personality disorders (defined in the DSM system) measured by any of a myriad of personality disorder assessment devices. Not only has the entire five-factor approach been subjected to trenchant methodological and substantive criticism (see Block, 1995, 2001, 2010; Franić, Borsboom, Dolan, & Boomsma, 2013; Shedler & Westen, 2004; Westen, 1996;), but the conceptualization of personality pathology as simply an extreme form of disagreeableness or neuroticism fails to capture to richness of these disorders, a richness well known to the experienced clinician and astute observers of this broad class of psychopathology.

A second model that sought to link personality factors to personality disorder was proposed by Cloninger et al. (1993). In this model, Cloninger and colleagues (Cloninger et al., 1993) proposed a model of normal personality thought to consist of two broad subsets of multidimensional domains. The first domain is made up of what are referred to as temperament dimensions and the second is referred to as character dimensions. Temperament consists of harm avoidance, novelty seeking, reward dependence, and persistence. The character domain is argued to consist of self-directedness, self-transcendence, and cooperativeness. According to this model, PD is thought to be reflective largely of low levels of self-directedness, a so-called character dimension (Cloninger et al., 1993). Specifically regarding BPD (and all other forms of personality disorder), Cloninger's framework asserts the disorder is reflective of low levels of self-directedness (a character feature) and high levels of both novelty seeking and harm avoidance. The Cloninger model and its associated measurement strategy suffer from a variety of marked conceptual and technical flaws, but these are beyond the scope of this discussion (see Depue & Lenzenweger, 2005; Farmer & Goldberg, 2008a, 2008b; Stallings et al., 1996; Waller et al., 1991). Research on BPD features in relation to the Cloninger temperament and character dimensions—specifically, the predicted correlations between BPD and low self-directedness, high novelty seeking and high harm avoidance—reveals only modest inconsistent support for the model (see Barnow et al., 2007, for review).

Finally, the third model under consideration is one that that has viewed personality disorder largely in terms of subsyndromal or preclinical expressions of liabilities for major forms of psychopathology (i.e., psychotic illness, affective disorders, and so on). Continuing with our illustrations using BPD, Siever and Davis (1991; see also Siever & Weinstein, 2009) proposed that BPD and the other Cluster B PDs (histrionic, antisocial, narcissistic) are variants of affective disorder. BPD, in this approach, is viewed essentially as a subsyndromal variant of affective illness marked by affective instability as a central criterion as well as high levels of impulse dyscontrol and aggression. This position regarding borderline pathology—positing a connection between BPD and major affective illness processes—has received only mixed support in the literature (cf., Gunderson & Phillips, 1991 vs. New, Triebwasser, & Charney, 2008). The critical clinical and conceptual point with respect to the Siever and Davis (1991; Siever & Weinstein, 2009) position is that BPD is not really considered as a disorder of personality, rather, it is viewed as functionally a variant of Axis I psychopathology. This particular model fails to capture the interactive nature of the underlying neurobiological processes that set the stage for BPD, rather pathology is viewed in terms of deviations on separate psychological dimensions thought to be related to underlying neurobiologically mediated processes. The other personality disorders are also essentially explained in the Siever/Davis (Siever & Davis, 1991) approach as variants of underlying Axis I disorder liabilities. For example, the Cluster A (schizotypal, paranoid, schizoid) disorders are viewed as related to schizophrenia-liability via cognitive disorganization and the Cluster C (avoidant, compulsive, dependent) disorders are viewed as derivative of anxiety and anxiety threshold dysfunction. This model was originally proposed in 1991 and remains largely the same currently (see Siever & Weinstein, 2009).

A detailed consideration of the limits of the five-factor, Cloninger et al., and Siever/Davis approaches to personality pathology can be found in Depue and Lenzenweger (2001, 2005). What has been generally lacking from most models of personality disorder can be summed up in a straightforward manner: (1) conceptualization of PD as a complex emergent end product of interacting processes; (2) clear instantiation of the personality systems underpinning PD in neurobehavioral systems; (3) thorough consideration of the impact of both genetic and epigenetic factors on the development of PD; and (4) thoughtful inclusion of environmental inputs (e.g., severe trauma) in interaction with the liability/predisposition to PD defined by the underlying neurobehavioral systems. We present an alternative model in this context for consideration in understanding BPD specifically as well as all PDs, more generally (Depue & Lenzenweger, 2001, 2005, 2006).

Brief Overview of the Attempted Redefinition of Personality Disorder in the *DSM-5*

There have been many discussions of the manner in which the American Psychiatric Association's Task Force on Personality Disorders labored to redefine the nature of personality pathology and the manner in which it should be diagnosed in the recently released *DSM-5*. The various professional perspectives as well as the theoretical, clinical, and political concerns that attended these discussions will not be repeated here as they are readily available in the published literature across many journals. An excellent overview summary of the entire attempted revision process of the personality disorders section of the DSM can be found in Krueger (2013; see also Lenzenweger, 2012). What is worth noting is that the system that was proposed as an alternative to the long-standing description of individual personality disorders contained in the various *DSM* systems (*DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR*) was rejected by both the Scientific Committee of the *DSM-5* Task Force, as well as the American Psychiatric Association's Board of Trustees. Thus, what one sees in the *DSM-5* in terms of personality disorders definitions and the manner in which diagnosis of PD is to be done are simply the exact same as those contained in the *DSM-IV-TR*. The core of the proposed PD model for the *DSM-5*, which was subsequently rejected by the APA, focused on (1) the degree of distortion present in self and other relations (an interpersonal conception that emphasizes both agency and communion as important dimensions of personality); and (2) a system of five broad domains of pathological personality specifiers (or traits). Personality disorder in the proposed model for the *DSM-5* used both of these elements to serve as the basis for describing and diagnosing PD (see Krueger, 2013, for excellent overview). The proposed revision also retained six personality disorder types defined by relatively unique patterns of impairments and traits—all readily recognizable from prior *DSM* systems—borderline, obsessive-compulsive, avoidant, schizotypal, antisocial, and narcissistic personality disorders. The revised approach represented what has been termed a *hybrid dimensional categorical model* and can be found in the appendix (also known as Section III) of the *DSM-5*. What is striking, from our theoretical perspective, is that the proposed (but not adopted) model for defining and diagnosing PD in *DSM-5* still largely viewed personality descriptors as simply associated traits of PD, rather than defining PD explicitly in terms of those underlying neurobehavioral systems giving rise to personality descriptors or traits. That said, the proposed system for *DSM-5* showed an increased awareness of the centrality of interpersonal dysfunction for personality pathology (see Krueger, 2013), which echoes not only our long-standing view regarding the centrality of the affiliation system in personality pathology (see below and Depue & Lenzenweger, 2001, 2005) but also a similar sentiment proposed by others (e.g., Gunderson & Lyons-Ruth, 2008; Hopwood, Wright, Ansell, & Pincus, 2013).

A Dimensional, Multivariate Framework of Personality Disturbance

As we argued recently (Depue & Lenzenweger, 2005), with the exception of schizotypal and paranoid disorders, it is no longer possible to accept the notion that personality disorders (PDs) represent distinct, categorical diagnostic entities. The behavioral features of PDs are not organized into discrete diagnostic entities, and multivariate studies of behavioral criteria fail to identify factors that resemble existing diagnostic constructs (Livesley, 2001). Indeed, just the opposite is observed: the behavioral features of PDs merge imperceptibly in a continuous fashion across diagnostic categories, resulting in a) significant overlap of behavioral features across categories and hence diagnostic comorbidity within individuals, and b) symptom heterogeneity within categories and hence frequent (and most common in some studies) application of the ambiguous diagnosis of personality disorders not otherwise specified (Livesley, 2001; Saulsman & Page 2004; see also Lenzenweger, 2008). Moreover, aside from schizotypy/schizotypic disorders (Lenzenweger, 2010), the existing latent class and taxometric analysis literature on PDs generally does

not provide support for distinct entities in the PD realm, and some provisional taxonic findings for borderline and antisocial PDs are open to doubt. It is, accordingly, not surprising that diagnostic membership is not significantly associated with predictive validity as to prognosis nor psychological or pharmacological treatments (Livesley, 2001).

Such a state of affairs supports proponents of a dimensional approach to PDs, who note that (1) the behavioral features of PDs not only overlap diagnostic categories, but also merge imperceptibly with normality (Livesley, 2001; Saulsman & Page, 2004); and (2) the factorial structure of behavioral traits associated with PDs is similar in clinical and nonclinical samples (Reynolds & Clark, 2001). Furthermore, the higher order structure of PD traits resembles four of the five major traits identified in the higher order structure of normal personality (Reynolds & Clark, 2001). These findings suggest that PDs may be better understood as emerging (*in an interactive manner*) at the extremes of personality dimensions that define the structure of behavior in the normal population (Depue & Lenzenweger, 2005).

The realization that personality dimensions should be related to conceptualizations of personality disorder or disturbance has led to innumerable attempts to illustrate the association of personality traits to PD diagnostic categories. Most of these prior studies, as noted above, have relied on the five-factor model of personality, which defines a structure characterized by the higher order traits of extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience. A recent meta-analysis demonstrated the limitation of the approach of correlating the first four traits with PDs (Openness was uncorrelated with any category; Saulsman & Page, 2004). The meta-analysis showed: (1) the correlation of these four traits with PD categories is moderate to weak; (2) the complex entity of a PD category is defined by as little as one trait but never by four traits in a significant way; and (3) single traits (especially neuroticism) characterize more than one, sometimes several, putatively distinct PDs. How helpful is it to know that Histrionic PD is characterized by moderately high extraversion but by no other trait; or, similarly, that Dependent PD is associated with moderately high neuroticism but with no other trait. Furthermore, the problem in this approach does not appear to be explained simply by use of a small number of broad traits. When the 30 facet scales of the NEO-PI were correlated with PD categories, only modest gains were achieved relative to the use of the four major traits (mean difference in $R^2 \sim 0.04$) (Reynolds & Clark 2001). What the meta-analysis did reveal is that most PDs manifest, in common, higher trait levels of neuroticism and lower trait levels of agreeableness, meaning that most individuals with PDs are subject to negative emotionality, heightened stress reactivity, and impaired interpersonal behavior. Thus, *when PD categories serve as the outcome variable*, personality traits provide little in the way of power to discriminate between such categories or to inform the issue of dimensional continuity from personality traits to states of disorder.

On the basis of the above discussion, we have argued that personality *disorders* as discrete disease entities do not exist per se (Depue & Lenzenweger, 2005). As an alternative, we proposed a new perspective, where personality disturbance represents emergent phenotypes that arise from the interaction of extreme values on critical subsets of major personality traits. That is, each individual's personality represents the interaction of all major traits. (In this context we note that the term *emergent* is used to describe personality disorders as configurations of disturbance that emerge or arise from the novel combination of constituent components, but such configurations of disturbance cannot be reduced readily to these contributing components. For example, one might think of the experience of consciousness or visual imagery as emergent properties of the brain (or, more specifically, neural circuits and structures within the brain) (cf., Rumelhart, 1984). Where individuals lie at the extreme (low or high) ends of interacting trait dimensions on subsets of the major traits, emotional behavior emerges that generates social or occupational impairment, rendering disturbance in the individual's life resulting from personality factors. This model follows from the position that higher order traits of personality reflect the activities of neurobehavioral systems (Depue, 2006; Depue & Collins, 1999; Depue & Morrone-Strupinsky, 2005). Though genetically speaking it may be possible to conceive of the neurobiological variables associated with neurobehavioral systems as subject to independent influences, it is impossible to imagine that these systems are independent at a functional level. Neurobehavioral systems, and the personality traits that reflect their influence, interact to produce complex behavior patterns—personality as a whole—in a multivariate fashion. Although this model is dimensional in nature, where personality disturbance lies at the extreme of normal, interacting personality dimensions, no assumption is made herein that phenotypic dimensions of personality are genetically continuous. The phenotypic continuity could well represent several underlying *distinct* genotypic distributions, as may be the case even within the normal range of variation of some personality traits (Depue, 2006).

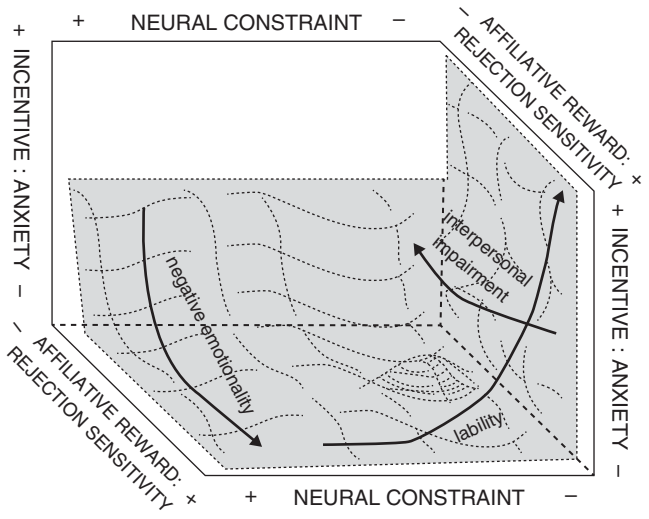


Figure 24.1 A multidimensional model of personality disturbance.

This multidimensional model of personality disturbance is illustrated in Figure 24.1. In the model, the axes are defined by neurobehavioral systems (which we will explicate later) rather than by personality traits, because traits are only approximate, fallible estimates of these systems. In Figure 24.1, behavioral approach based on positive incentive motivation (thought to underlie extraversion and positive emotionality, Depue & Collins, 1999) and anxiety/stress reactivity (thought to underlie neuroticism and negative emotionality, Canli, 2008; Depue & Lenzenweger, 2005) are modeled as a ratio of their relative strength, because the opposing nature of their eliciting stimuli affects behavior in a reciprocal manner, such that the *elicitation* or *expression* of one system is influenced by the strength of the other. The affiliative reward dimension (representing the capacity to experience consummatory reward from social and soft-touch stimulation, and thought to underlie the trait of social closeness or agreeableness, Depue & Morrone-Stupinsky, 2005) is placed in ratio with rejection sensitivity in the model, because they both largely influence the interpersonal domain, but can have opposite effects on social bonding. Moreover, a dimension of rejection sensitivity likely provides a novel contribution to dependent-, avoidant-, and borderline-like disturbance (all high on this dimension). The neural constraint dimension (thought to underlie the trait of constraint or conscientiousness) modulates the expressive features (especially the threshold of stimulus elicitation) of the other systems (Carver & Miller, 2006; Depue & Lenzenweger, 2005; Spoont 1992). Due to the limitation of graphing more than three dimensions, it should be noted that the model includes one additional system/trait that we suggest influences the manifestation of personality disturbance: the ratio of affective aggression:fear is necessary to account for the full range of antisocial (high aggression:low fear) behavior. Taken together, then, the model proposes that the interaction of at least six neurobehavioral systems underlying dimensional personality traits are necessary to account for the emergent phenotypes observed in personality disturbance.

Two significant features of the model are worth emphasizing. First, the phenotypic expression of personality disturbance, represented by the gray-shaded *reaction* surface in the figure (accounting for ~10% of the population; Livesley, 2001), is continuous in nature, changing in character gradually but seamlessly across the surface in a manner that reflects the changing product of the multidimensional interactions. It may be that certain areas of the surface (i.e., certain system/trait interactions) are associated with increased probability (risk) of certain features of personality disturbance (perhaps having led to clinical theories of PDs based on prototypic phenotypes), and this is represented in the right-back area of the figure as an elevation in the surface that is continuous rather than distinct in contour. This representation, however, is not meant to imply that a distinct disorder exists in that particular area of the surface.

Second, the extent and positioning of the gray reaction surface is weighted most heavily by *increasing* anxiety/stress reactivity, *decreasing* neural constraint, and *decreasing* affiliative reward:*increasing* rejection sensitivity. This weighting is also reflected in the lines with directional arrows overlaying the gray surface in the figure, which illustrate increasing phenotypic negative emotionality, emotional lability, and interpersonal impairment. These three factors were found to be the most common characteristics of all PDs in the meta-analysis of Saulsman and Page (2004), and a recent study showed independent genetic contributions to these factors (Kendler et al., 2008), thereby empirically supporting their emphasis in the model.

Implications of the model are discussed in detail elsewhere (Depue & Lenzenweger, 2005), but one seems important in the consideration of the *development* of personality disturbance: sex differences in some forms of personality disturbance may imply differential risk (neurobiologic or environmental) based on gender. The increased prevalence of males with antisocial behavior may reflect the higher mean of males in the population on the ratio of traits of aggression:fear and a lower mean on constraint (Spoont, 1992). Additionally, the increased prevalence of females with borderline- and dependent-like personality disturbance may reflect a combination of

(1) their higher mean on both trait anxiety; (2) their higher mean on social closeness, thereby increasing the need for social relationships whose loss is feared; (3) their higher mean on rejection sensitivity, thereby increasing their vacillation between dependence and rejection of others; (4) their lower mean on extraversion, particularly social dominance, hence enhancing the predominance of high levels of trait anxiety; and (5) their lower mean on the ratio of aggression:fear, hence decreasing the prevalence of antisocial behavior (Depue & Collins, 1999; Depue & Morrone-Strupinsky, 2005; Tellegen & Waller, 1997).

Developmental Implications of the Model

Viewing the phenotypic expression of personality disturbance within the concept of a *reaction surface* in Figure 24.1 implies that an individual's expression of disturbance is variable across time, waxing and waning with fluctuations in environmental circumstances, stressors, and interpersonal disruptions. Indeed, Lenzenweger demonstrated in a longitudinal assessment of the stability of formally defined personality disorders that phenotypic intensity varied markedly over time, thereby affecting the presence/absence of diagnostic status as well as level of symptomatology (Lenzenweger et al., 2004). This implies that one's multivariate value on the reaction surface represents a risk or potential for personality disturbance whose full expression is dependent on current life circumstances. Furthermore, that risk or potential is accordingly variable over time as well. An individual's mean level on personality traits is a function of multiple genetic and environmental variables, in keeping with recent models of the development of psychopathology (Cicchetti, 2007), and the interaction of these variables over the life span may modify the extremity of an individual's level in enduring ways. In this way, *developmental* experience can substantially modify an individual's level on personality traits, and may contribute to an individual's position with respect to the reaction surface.

In our subsequent discussion of these experiential effects on the neurobehavioral systems underlying personality traits, it is helpful to first define a framework of how experiential factors interact with neurobiological variables to determine personality trait levels. In so doing, we will use neuroticism—defined as anxiety, stress reactivity, and negative emotionality—as an example. As shown in Figure 24.2, an individual's trait level of expressed anxiety and negative emotion is dependent on the individual's characteristic minimum threshold of stimulus elicitation of a neurobiological variable associated with anxiety/stress reactivity. This minimum threshold represents a central

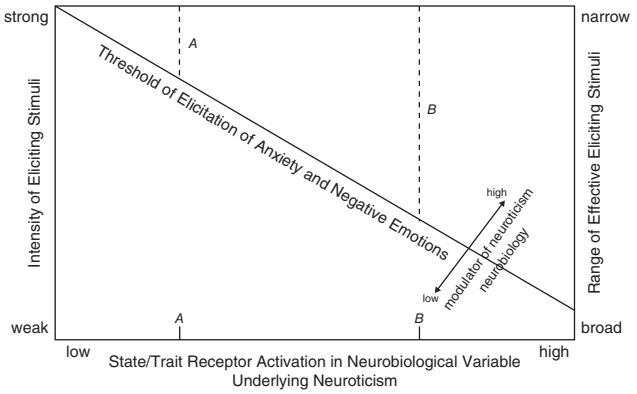


Figure 24.2 A minimum threshold for elicitation of anxiety and negative emotions is illustrated as a trade-off function between eliciting stimulus magnitude (left vertical axis) and postsynaptic receptor activation of a neurobiological variable underlying the personality trait of neuroticism (horizontal axis). Range of effective (eliciting) stimuli is illustrated on the right vertical axis as a function of level of receptor activation. Two hypothetical individuals with low and high *trait* postsynaptic receptor activation (demarcated on the horizontal axis as *A* and *B*, respectively) are shown to have narrow (*A*) and broad (*B*) ranges of effective stimuli, respectively. Threshold effects due to a modulator of neuroticism neurobiology are illustrated as well.

nervous system weighting of the external and internal factors that contribute to initiation of the processes associated with anxiety (Depue & Collins, 1999). Generally, the threshold is weighted most strongly by the joint function of two main variables: (1) magnitude of anxiety-inducing stimulation; and (2) level of postsynaptic receptor activation by the neurotransmitters or neuropeptides that mediate the effects of the stimulus in facilitating anxiety. The relation between these two variables is represented in Figure 24.2 as a trade-off function, where pairs of values (of stimulus magnitude and receptor activation) specify a diagonal representing the minimum threshold value for activation of a behavioral or emotional process, in this case anxiety and negative emotions. Because the two input variables are interactive, independent variation in either one not only modifies the probability of behavior, but it also simultaneously modifies the value of the other variable that is required to reach a minimum threshold. Finally, individual variation in variables that significantly interact with the functioning of the anxiety-facilitating neurotransmitter would serve as a source of modulation of the threshold. We discuss this further under the section on constraint.

A *trait* dimension of postsynaptic receptor activation by an anxiety-facilitating neurobiological variable is represented on the horizontal axis of Figure 24.2, where two

individuals with divergent trait levels are demarcated: *A* (low trait level) and *B* (high trait level). Trait levels would be determined by genetic factors that affect the functional activity of the neurobiolgoical variable, as well as by developmental experiences that modify gene expression (e.g., by affecting receptor availability). These two divergent individuals may be used to illustrate the effects of trait differences in both acquisition and maintenance of anxiety, stress reactivity, and negative emotionality.

As Figure 24.2 indicates, for any given stimulus, the degree of *state* (contemporaneous, stimulus-induced) neural response (receptor activation) will on average be larger in individual *B* versus *A*. Our proposal is that this differential responsivity is a major source of the neurobiological basis of the *temperamental* (i.e., nonexperiential) component of anxiety and, hence, of variation in the acquisition of stimulus control and levels of anxiety. Because the degree of state neural activity is correlated with the magnitude of *subjective emotional experiences* that are naturally elicited by stimuli, negative emotionality is also predicted to be more enhanced in *B* vs *A*.

This difference between individuals *A* and *B* in magnitude of stimulus-induced neural activation and accompanying subjective emotional experience may contribute to two important sources of variation in the *development* of anxious, stress reactive behavior. First, as noted above, independent variation in either of the two interactive variables that determine threshold (neural activation and magnitude of the stimulus) also simultaneously modifies the value of the other variable that is required to reach a minimum threshold. This suggests that the enhanced negative emotion induced by stimuli in individual *B* will result in an equally enhanced negative encoding in memory of that anxiety-inducing stimulus relative to individual *A*.

Second, if individual differences in emotional encoding apply across the full range of magnitudes of stimuli, trait differences in neural activation may have marked effects on the range of effective (i.e., anxiety-inducing) stimuli. This is illustrated in Figure 24.2, where the right vertical axis represents the range of effective stimuli. Increasing trait levels of neural activation (horizontal axis) are associated with an increasing efficacy of weaker stimuli and, thus, with an increasing range of effective stimuli. In Figure 24.2 individuals *A* and *B* are shown to have a narrow vs broad range, respectively. Significantly, the broader range for individual *B* suggests that on average *B* will experience more frequent stimulus elicitation of anxiety, stress, and negative emotions. This means that the probability at any point in time of being in an anxious, stressed state for individual *B* is higher than for *A*. Therefore, when subsequent stimuli are encountered, their subjectively evaluated emotional magnitude will show a stronger negative bias for *B* than *A*. Thus, trait differences in thresholds may *proactively* influence the evaluation and encoding of stimuli, and may not be restricted to *reactive* emotional processes.

Such a perceptual/attentional bias for negative, anxiety-eliciting cues may be mediated by the basolateral nuclei of the amygdala. Crude representations of anxiety-associated cues can reach the basolateral nuclei via monosynaptic projections from the thalamus within ~10 msec without awareness. This input then activates a dense network of backprojections from the basolateral nuclei to many regions of the brain, including those that process sensory representations, thereby facilitating the processing specifically of anxiety-producing cues. The enhanced negative encoding in memory in the basolateral amygdala of such cues by individual B throughout development would lead to frequent, rapid activation of the amygdala when such cues were reexperienced, and in turn a perceptual/attentional biasing of anxiety cues of even weak magnitude via the amygdala's backprojections.

The overall manifestation of these various processes is likely to be more frequent negative emotional experience for individual *B* relative to *A*. A broader range of effective, anxiety-producing stimuli, each with enhanced negative emotional encoding, is expected to produce more robust neural reactivity to stimuli in individual *B*. Accordingly, an enhanced acquisition of a broader array of conditioned stimuli that become associated with anxiety-producing contexts can be expected for individual *B*. Thus, variation in neural activation by stimuli may not only influence the level of negative emotion, but also may lead to variation in the strength of associative processes that link neutral stimuli with negative emotional contexts. *The outcome of these interactions may be the acquisition of a more elaborate associative network of negative emotional environmental contexts in individual B, leading to* different *developmental trajectories* in anxiety and stress reactivity for individuals *A* and *B*.

In the discussion that follows, we will briefly review the neurobehavioral systems that underlie the major personality traits, and focus more substantially on the evidence that they are subject to experience-dependent modification that can be enduring through the effects of experience on genetic expression, mainly through processes known as epigenetics. It is through such processes that risk for personality disturbance may be modified by experience at any point in development, but perhaps especially during early critical periods of development. Due to the fact that this research

has been inordinately focused on anxiety and stress reactivity, the *neuroticism* section will be most extensive relative to other traits. This seems appropriate, however, since the trait of neuroticism is the strongest associate of most PDs.

NEUROBEHAVIORAL SYSTEMS UNDERLYING HIGHER ORDER PERSONALITY TRAITS AND THEIR MODIFICATION BY EXPERIENCE

We focus on the five major traits in Figure 24.1 which are robustly identified in the psychometric literature: *neuroticism*, *extraversion*, s*ocial closeness* or *agreeableness*, *rejection sensitivity*, and *constraint or conscientiousness*. We will define below coherent neurobehavioral systems for each of these traits, and evidence indicating that they are significantly modified by experience.

Neuroticism

Fear versus Anxiety

Adaptation to aversive environmental conditions is crucial for species survival, and at least two distinct behavioral systems have evolved to promote such adaptation. One system is fear (often labeled harm avoidance in the trait literature), which is a specific behavioral system that evolved as a means of escaping unconditioned aversive stimuli that are inherently dangerous to survival, such as tactile pain, injury contexts, snakes, spiders, heights, and sudden sounds. These stimuli are specific, discrete, and explicit, and in turn elicit specific, short-latency, high-magnitude phasic responses of autonomic arousal, subjective feelings of panic, and behavioral escape. Specific, discrete neutral stimuli associated with these unconditioned events elicit conditioned fear.

There are, however, many situations in which specific aversive cues do not exist, but rather the stimulus conditions are associated with an elevated *potential* risk of danger or aversive consequences. In such cases, no explicit aversive stimuli are present to inherently activate fear circuitries. Nevertheless, the stimuli can be unconditioned in nature, as in darkness, open spaces, unfamiliarity, strangers, and predator odors, or they can be conditioned contextual cues (general textures, colors, relative spatial locations, sounds) that have been associated with previous exposure to specific aversive stimuli. Conceptually, these stimuli are characterized in common by unpredictability, uncontrollability, unavoidability, unfamiliarity—or, more simply, *uncertainty*, which are the same stimulus features that characterize what is referred to as stress.

To reduce the risk of danger in such circumstances, a second behavioral system evolved, *anxiety*. Anxiety is characterized by negative emotions (anxiety, depression, hostility, suspiciousness, distress) that serve the purpose of informing the individual that, though no explicit, specific aversive stimuli are present, conditions are potentially threatening (White & Depue, 1999). This affective state, and the physiological arousal that accompanies it, continues or reverberates until the uncertainty is resolved. It is this prolonged negative state of anxiety that distinguishes its subjective character from the rapid, brief state of panic and fear associated with the presence of a specific fear stimulus. Associated responses that may functionally help to resolve the uncertainty are heightened attentional scanning of the uncertain environment and cognitive worrying and rumination over possible response–outcome scenarios. Thus, anxiety represents a general behavioral system that is activated by a broad *class* of stimulus (uncertainty), whereas fear represents a more specific behavioral system that evolved to respond to specific stimuli critical for survival. The trait literature supports the *independence* of anxiety and fear, which as personality traits are completely uncorrelated and are subject to distinct sources of genetic variation (Tellegen et al., 1988; White & Depue, 1999).

Neurobiology of Anxiety and Stress Reactivity

The neurobehavioral system of anxiety is represented in the higher order traits of personality by *neuroticism*, which is characterized by negative emotions, a heightened and persistent state of stress reactivity, and interpersonal alienation. Animal and human research have identified three neurobiological pathways that are associated with anxiety, stress reactivity, and neuroticism, which is consistent with the systems theory concept of multifinality (Cicchetti & Dawson, 2002): a genetic polymorphism in the gene that codes for the serotonin transporter, the central corticotrophin-releasing hormone (CRH) system, and the peripheral glucocorticoid system. Furthermore, all three are subject to modification by adverse events in early development.

1. Serotonin Transporter

Serotonin Transporter and Neural Circuitries Following release serotonin (5-HT) is deactivated by being taken back up into the presynaptic terminal and is then restored in vesicles. This uptake process requires active transport across the presynaptic membrane by the 5-HT transporter (5-HTT) residing in that membrane. As shown in Figure 24.3, there is a polymorphism in the promotor region of the gene (SLC6A4) that codes for 5-HTT that

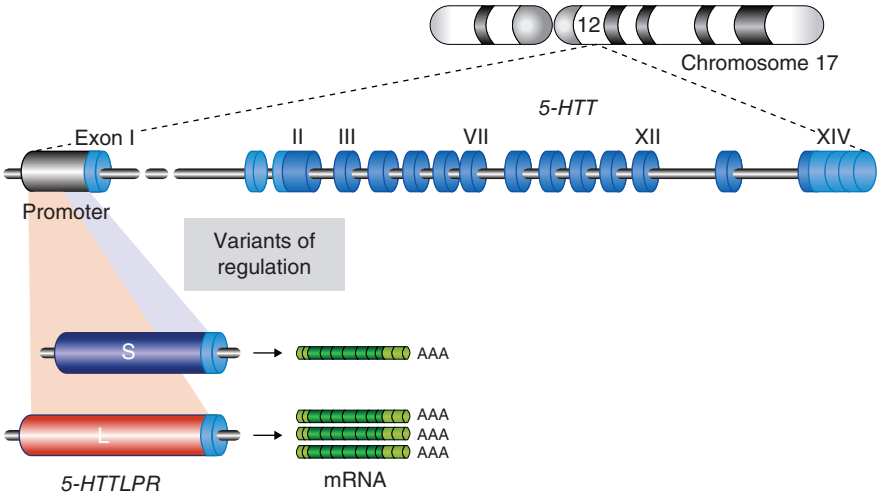


Figure 24.3 Illustration of the components of the gene (SLC6A4) that codes for the serotonin transporter (5-HTT). Polymorphism of the promotor region yields two common alleles (S and L) that differ in length of nucleotide number. See footnote 1.

results in two common alleles, referred to as long (l) and short (s) alleles since their respective promotor regions differ in number of nucleotides (Lesch & Canli, 2006). Due to the facilitatory effects of the promotor region on gene production, the l-allele codes for more RNA and therefore produces more transporter protein than the s-allele. The s-allele is characterized by reduced 5-HTT promotor activity and 5-HTT expression, resulting in a reduced rate of removing 5-HT from the synaptic cleft and increased extracellular levels of 5-HT.

At the behavioral level, 5-HTT knockout mice exhibit increased anxiety and reduced exploration, and primates and humans with the s-allele (or the homolog of it in primates) express increased behavioral anxiety, increased scores on neuroticism scales, increased risk of depression, less effective responses to SSRI treatment, and reduced social closeness (Hariri, 2006). At the neural level, the s-allele has been associated with both neural function and structure. The s-allele has been consistently found to be associated in both males and females with enhanced amygdala reactivity to many forms of emotional stimuli, including fear and angry faces, and negative scenes and words (Canli & Lesch, 2007; Hariri, 2006). In addition, the s-allele is associated with reduced gray matter volume in the amygdala, suggesting reduced dendritic branching and axonal arborization (Hariri, 2006). Thus, there is a link between gene variation and basic brain mechanisms involved in processing negative emotion.

The reduced gray matter volume and increased reactivity of the amygdala in s-allele carriers (both S/S and L/S) raises the possibility that the amygdala's neural circuitry interactions may be influenced (i.e., its projections to and

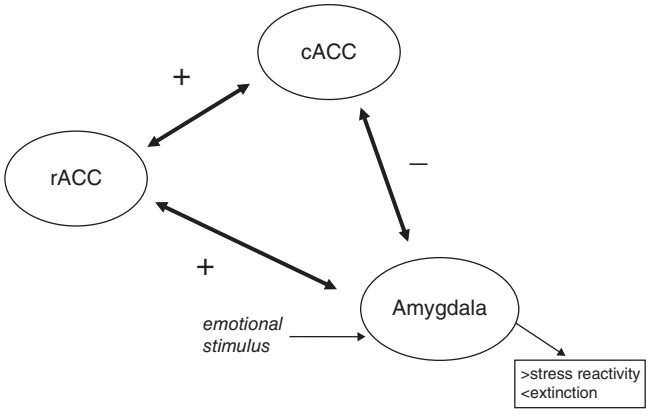


Figure 24.4 Anterior cingulate–amygdala circuitry that provides negative feedback to modulate activity of the amygdala.

efferents from other brain regions). Indeed, recent research on the anterior cingulate cortex (ACC)–amygdala circuitry confirms this possibility. Specifically, the perigenual portion of the ACC, which surrounds the genua of the corpus collosum, is composed of the subgenual, rostral rACC and the supragenual, caudal cACC. As shown in Figure 24.4, the rACC receives the densest projections from the amygdala, conveys that information to the cACC, which in turn sends efferents back to the amygdala. This circuitry is critical to modulating amygdala reactivity via inhibitory feedback from cACC to the amygdala during times of emotional stress.

Pezawas et al. (2005) found psychiatrically normal s-allele carriers to have reduced gray matter volume of both the perigenual ACC and the amygdala, with the most pronounced reduction in the rACC region, and a

reduced covariance of pACC (especially rACC)–amygdala volumes. Furthermore, during the processing of fear and angry faces, there was greatly reduced positive covariance between rACC–amygdala activation, and reduced negative covariance between cACC–amygdala activation, suggesting a reduced negative feedback of the cACC on amygdala reactivity to stressful stimuli. Covariance between rACC–amygdala activation accounted for ~30% of the vairance in neuroticism scores in the entire sample, whereas no single region was significantly related to neuroticism. Thus, it is the reduced coherence of activity across brain regions associated with the s-allele that most markedly affects enhanced reactivity to stress.

The implications of amygdala overreactivity are consistent with the phenotypic features of neuroticism. One can expect the persistent increased arousal being conveyed by amygdala efferents to other brain regions to be associated with anxiety and feelings of distress, persistent enhancement of vigilance for threat, increased rumination of negative thoughts, increased acquisition of negative emotional memories, and decreased extinction of anxiety elicited by environmental contexts. The s-allele creates a reduced threshold for stimulus-induced arousal in the amygdala that is dependent on less coherent activity within its interactions with perigenual ACC circuitry. This state of persistent overreactivity apparently creates an enhanced risk for anxiety and depressive disorders in s-allele carriers, but only under conditions of stressful life events or early adverse experience such as childhood maltreatment (Caspi et al., 2003).

Serotonin and Development of Neural Connections The altered coherence in gray matter volume and functional activity in the pACC–amygdala circuitry, implying reduced dendritic branching and axonal arborization, suggests the possibility that the s-allele modifies connections between brain regions. Significantly, 5-HT plays a critical role in the development and plasticity of the brain (Gaspar et al., 2003). 5-HT neurons are among the earliest neurons to be generated prenatally, appearing in the first embryonic month in primates. Knockout of the 5-HT system prenatally results in no gross wiring or structural effects, but 5-HT is used as a later developmental signal, which modulates construction and plasticity of brain circuits. Major pre- and postnatal developmental effects of 5-HT include modulation of dendritic length and number of spines, and axon arborization: that is, the development of selected brain circuits.

Pre- and postnatal developmental effects of 5-HT arise from two sources. First, there is direct release of 5-HT from brainstem raphe (where 5-HT synthesizing neurons are localized) projections to cortical target regions. Second, glutamate neurons, which comprise the main excitatory neurons that interconnect brain regions, in the process of developing thalamic–limbic and cortico-cortical efferents capture 5-HT via transient axonal expression of the 5-HT transporter. 5-HT is then released at thalamocortical and cortico-cortical synapses to enhance presynaptic axon arborization and postsynaptic dendritic processes, again enhancing neural circuitries. This represents, then, one of the means by which l- and s-allele variation could make a significant difference in interconnections between brain regions.

The effects of 5-HT during development are dependent on which 5-HT receptors are activated. There are 4 groupings of these receptors. 5-HT1A autoreceptors, localized to soma and dendrites of raphe nuclei, and 5-HT2A receptors, one of the most widely expressed in the brain, are expressed late in development and enhance dendritic processes. 5-HT2A receptors also modulate the expression of the Bdnf (brain-derived neurotrophic factor) gene in neocortex and hippocampus. Bdnf secretion from postsynaptic neurons in response to neurotransmitter activation of postsynaptic receptors sculpts glutamate innervation patterns of dendrites and axons, increases synaptic efficacy of glutamate, and modulates LTP in the hippocampus. Thus, 5-HT2A receptor activation can in this indirect way modulate dendritic and axonal processes. On the other hand, 5-HT1B and 5-HT2C receptors are mainly localized to axons and axon terminals, enhancing synaptic strength via axon arborization of glutamate axonal connections through enhanced release of glutamate.

This 5-HT modulation has its strongest effects during development as opposed to later in life (Ansorge et al., 2004; Gaspar et al., 2003; Gross & Hen 2004; Leonardo & Hen 2006). In rodents, the forebrain has an experience-expectant period of dramatic synaptogenesis and dendritic growth 3–4 weeks postnatally, and hippocampal maturation of dendritic branches occurs during 2–4 weeks postnatally. In primates, this period corresponds to early postnatal months. The 5-HT1A receptor also appears in week 2 postnatally in hippocampus, amygdala, and ACC, and, if knocked out or blocked in the first 4 weeks in the early postnatal period, there is a strong enhancement of adult anxiety which first appears in week 3—but no anxiety enhancement occurs when the receptor is blocked in adulthood (Lesch & Canli, 2006; Tsetsenis et al., 2007). 5-HT1A autoreceptors enhance dendritic maturation, and thus their blockade could affect neural circuitry; whereas 5-HT1A postsynaptic receptors induce hyperpolarization and reduce neuronal excitability

in postsynaptic neurons—thus increasing the threshold for firing the postsynaptic neuron. Blockade of this latter effect could contribute to amygdala overreactivity. These findings suggest that 5-HT mediation by 5HT1A receptors is essential to the establishment of normal anxiety-modulating circuits in the brain during early postnatal development. Knockout of monoamine oxidase A (MAOA), which provides the main degradation of 5-HT after reuptake, increases 5-HT inordinately, and has many developmental effects, but only when it is knocked out in the early postnatal period (Gaspar et al., 2003). Consistent with these biochemical findings is that adverse rearing environments in monkeys (Champoux et al., 2002) and in humans (Taylor et al., 2006) interact with the 5-HTT polymorphism, where the effects of the s-allele on anxiety and depression is enhanced by environment.

In sum, then, it is hypothesized that the 5-HTT polymorphism affects 5-HT–modulated development of dendritic and axonal development and fine-tuning of connectivity patterns in the forebrain. Variation in the connectivity of the pACC–amygdala circuits manifests neurally as amygdala hyperreactivity to stress, and behaviorally as anxiety, stress reactivity, negative emotionality, and an increased risk for anxiety and depressive disorders in the context of accumulating environmental adversity. Risk factors that interact with 5-HT effects may be a polymorphic variation in the Bdnf gene (val Bdnf) that results in reduced Bdnf postsynaptic secretion and hence reduced synaptic connectivity; low levels of MAOA activity, increasing 5-HT presynaptic levels and release; and early environmental diversity.

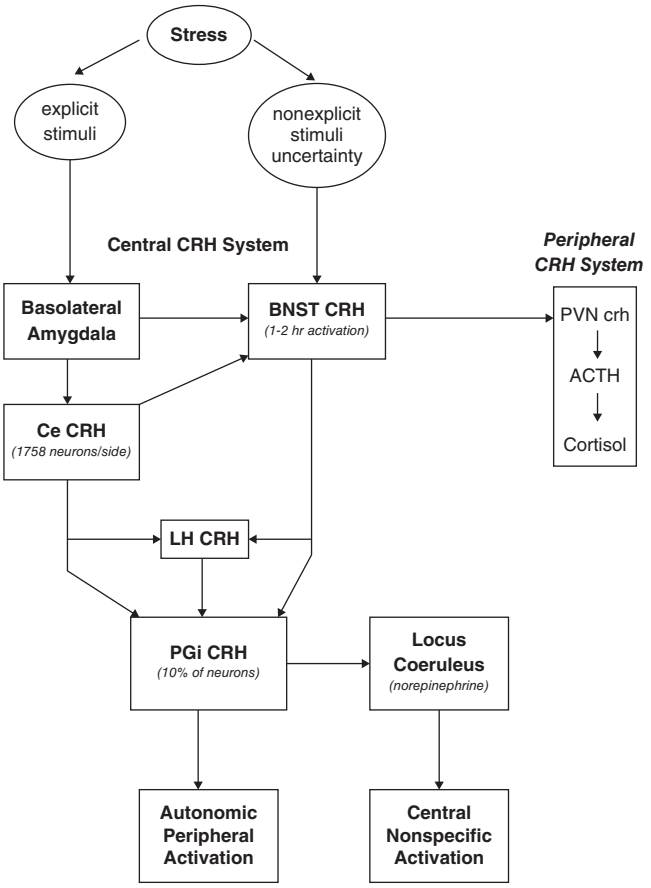


Figure 24.5 Components of the central and peripheral corticotrophin releasing-hormone (CRH) systems. Abbreviations: Ce (central amygdala nucleus), BNST (bed nucleus of the stria terminalis), LH (lateral hypothalamus), PGi (paragiganticocellularis), PVN (paraventricular nucleus of the hypothalamus), ACTH (corticotropic hormone from the anterior pituitary).

2. Central CRH Functioning

Central CRH and Anxiety As illustrated in Figure 24.5, the effects of stress are mediated by a central system of CRH neurons. Stressful contexts can include both explicit, discrete stimuli that generate fear and nonexplicit stimuli associated with uncertainty that generate anxiety. It is now well established that association of discrete, explicit neutral stimuli (fear CS) with an aversive UCS occurs via cortical uni- and polymodal sensory efferents that converge on the basolateral complex of the amygdala (Davis & Shi, 1999; Kalin et al., 2004; LeDoux, 1998). Fear CSs elicit a host of behavioral, neuropeptide, and autonomic responses via output from the basolateral amygdala to the central amygdala (Ce), which in turn sends functionally *separable* efferents to many hypothalamic and brainstem targets (LeDoux et al., 1998).

In contrast, the enduring potentiating effects of nondiscrete, contextually related aversive stimuli on anxiety (but not fear) is dependent on a group of structures collectively referred to as the *extended amygdala*, which receives massive projections from basolateral and olfactory amygdala complexes, and which represents a macrostructure that is characterized by two divisions, central and medial (Heimer 2003; Kalin et al., 2001). These two divisions originate from the central and medial nuclei of the amygdala, and consist of cell groups that are distributed throughout the sublenticular area, bed nucleus of the stria terminalis (BNST), around striatal and pallidal structures, and back to merge specifically with the caudomedial region of the nucleus accumbens.

The central division of the extended amygdala appears to associate *general contextual features and nonexplicit, nondiscrete* conditioned and unconditioned stimuli with reward or punishment (e.g., light conditions, physical features, spatial relations) (Davis & Shi 1999; McDonald

et al., 1999). Similar to the outputs from the Ce, most structures of the central division of the extended amygdala can transmit this motivationally relevant information to some or all hypothalamic and brainstem structures related to emotional expression (Heimer, 2003). This output coordinates activation of (1) the negative affective state of anxiety to inform the individual that the current context is uncertain and potentially dangerous; (2) autonomic arousal to mobilize energy for potential action; (3) selective attention to maximize sensory input at specified locations in the visual field; and (4) cognition to derive a response strategy. Thus, two emotional learning systems may have evolved: the basolateral amygdala to associate reinforcement with explicit, specific characteristics of objects (i.e., for fear), and the BNST to associate reinforcement with nonexplicit spatial and contextual stimulus aspects (i.e., for anxiety).

As indicated in Figure 24.5, the basolateral and central amygdala and the BNST provide integration of behavioral, neuroendocrine, and autonomic responses to stressful circumstances (Leri et al., 2002). This integration is accomplished by the activity of both the peripheral and central CRH systems. The *peripheral* system involves CRH neurons located in the paraventricular nucleus of the hypothalamus (PVN), which when activated initiates the series of events that ends in the release of cortisol from the adrenal cortex. Cortisol then circulates in the bloodstream and increases energy reserves (gluconeogenesis) and, if not excessive in quantity, can enhance neurotransmitters involved in modulating emotion and memory (Kim & Diamond, 2002).

In contrast, the *central* CRH system is composed of CRH neurons located in many different subcortical brain regions that modulate emotion, memory, and central nervous system arousal. Whereas the majority of CRH neurons in the CNS do not mediate the effects of stress, some of the CRH-containing regions that are important in mediating stress effects are illustrated in Figure 24.5. For instance, the basolateral amygdala detects discrete aversive stimuli associated with stressful circumstances and activates the extensive array of CRH neurons located in the Ce (~1750 neurons per hemisphere) (Merali et al., 2003). These CRH neurons project to many brain regions that modulate emotion, memory, and arousal, including the BNST and the peripheral CRH neurons in the PVN. Stress variables associated with context and uncertainty activate CRH neurons in the BNST, which have similar projection targets as the Ce (Macey et al., 2003). Both the Ce and the BNST can activate CRH neurons in the lateral hypothalamus (LH), a region that integrates CNS arousal as a means of modulating changes in the ANS. In turn, the LH CRH projections modulate ANS activity. Importantly, as illustrated in Figure 24.5, all three sources of CRH projections—the Ce, BNST, and LH—innervate CRH neurons in the paragiganticocellularis (PGi) (Aston-Jones, 1996), which is located in the rostral ventrolateral area of the medulla in the brainstem. The PGi is a massive nucleus that provides major integration of central and autonomic arousal and, in turn, coordinates and triggers arousal responses to urgent stimuli via two main pathways eminating from its own population of CRH neurons, which make up 10% of PGi neurons (Aston-Jones, 1996). One CRH pathway modulates the ANS via projections to the intermediolateral cell column of the spinal cord, activating sympathetic preganglionic autonomic neurons.

The other CRH pathway modulates central arousal effects via activation of the locus coeruleus (LC), where PGi CRH innervation of the LC in humans and monkeys is dense (Aston-Jones, 1996). The LC, which is composed of ~20,000 neurons that provide the major source of norepinephrine (NE) in the brain, innervates the entire brain. LC neurons that release NE onto *B*-adrenergic receptors are responsible for producing a nonspecific emotional activation via broadly collateralizing axons to the central nervous system (Aston-Jones, 1996), and this NE release to chronic stress is increased in inbred rat strains with high anxiety (Blizzard, 1988) and in posttraumatic stress disorder patients (Charney et al., 1998). This nonspecific emotional activation pattern comprises a global urgent response system that responds to unpredicted events and hence facilitates behavioral readiness, alerting (enhanced sensory processing), and attention (enhanced selection of stimuli) (Aston-Jones, 1996), which are all characteristic of states of anxiety in highly stress-reactive rodents and monkeys (Blizzard, 1988; Redmond, 1987). And this central arousal can be enduring: PGi CRH activation of LC neurons endures and peaks 40 minutes after stimulation of the PGi (Aston-Jones, 1996). This persistent activation of spontaneous activity in the LC renders the effects of short-lived, nonsalient stimuli of little effect on the LC, such that salient stimuli have an inordinate effect on LC activity and hence, in turn, on central activation. Thus, taken together, the central CRH neuron system is capable of activating a vast array of behaviorally relevant neural and hormonal processes during stressful conditions, including activation of the peripheral CRH system.

Early research demonstrated that CRH in the BNST rather than in the Ce mediates anxiety as opposed to fear, whereas the Ce expresses fear but not anxiety. Thus, injection of CRH into the BNST of rats potentiates startle (an index of anxiety) in a dose-dependent manner for up to

two hours duration (Davis & Shi 1999). Subsequent work has confirmed a specific role for CRH in the BNST in the mediation of anxiogenic effects. Intense inescapable stressors induce a persistent anxious state in rats characterized by increased sensory reactivity and enhanced associative learning with aversive UCSs. This is accompanied by elevated levels of CRH in the BNST. Marked anxiety effects lasting longer than 24 hours are produced after administration of three doses of CRH over 1.5 hours, despite no lasting effect on peripheral release of corticosterone (Servatius et al., 2005). The source of naturally occurring CRH in the BNST is from the Ce's population of CRH neurons: CRH release from the Ce after a psychogenic stressor causes long-term anxiety effects in rats, which correlates with CSF CRH concentrations (Merali et al., 2003).

The anxiogenic effects of CRH are specific to the lateral region of the BNST. Intra-lateral BNST (but not intra-Ce) administration of CRH in rats elicits dose-dependent anxiogenic effects via CRH-R1 receptors, including reduced exploration of an unfamiliar cage and an elevated T-maze (which are both aversive UCSs); reduced sleep, food intake, and sexual activity; and increased sympathetic and behavioral signs of anxiety (shaking, crouching, cautious approach) (Nie et al., 2004). Furthermore, intra-lateral BNST (but not intra-Ce) administration of CRH in rats provides a dose-dependent aversion to the CRH-paired environment via CRH-R1 receptors, indicating that the lateral BNST is a critical site for associative conditioning of context and aversive signals mediated by CRH (Sahuque et al., 2006). The CRH-R1 receptors in the forebrain mediate these anxiogenic effects. Transgenic mice with elevated CRH-R1 (but not with elevated R2) receptors in the central forebrain (but with no elevation peripherally in the hypothalamus or pituitary) show extreme indications of anxiety; whereas mice with knockout of the CRH-R1 (but not R2) receptor gene in the central forebrain (but not peripherally) show little anxiety in the elevated-T maze or in the light-dark test (both being aversive UCSs) (Deussing & Wurst, 2005). Moreover, conditional activation of CRH-R1 gene expression centrally (but not peripherally) produces *anxiogenic* effects, whereas conditional inhibition of CRH-R1 gene expression centrally (but not peripherally) produces *anxiolytic* effects. And finally, a CRH-R1 antagonist administered orally to male monkeys impaired development and expression of contextual anxiety conditioning, and blocked social stress-induced (two unfamiliar male monkeys placed in attached plexiglass cages) increases in anxiety behaviors, cortisol, CSF CRH concentrations, and locus coeruleus neuronal firing (Habib et al., 2000).

These findings taken together suggest that anxiety is essentially a stress response system that relies on a central network of CRH neuron populations acting via CRH-R1 receptors that provide integrated responses (hormonal, behavioral, autonomic and central arousal) to the stressor. CRH especially in the lateral BNST mediates what is a defining characteristic of anxiety as opposed to fear: *anxiogenic* effects, which last as long as uncertainty is unresolved, and aversive *contextual* conditioning. These CRH-induced psychological effects appear to strongly match the content of trait neuroticism measures, where the strongest primary or facet scale in the higher order factor of neuroticism in Tellegen's personality questionnaire is termed *stress reactivity* due to the persistent negative emotional responses reported to stress-related events in items loading on the scale (Tellegen & Waller, 1997).

Finally, although trait levels of neuroticism are very stable over as many as 20 years, it is less stable up to adolescence. This suggests that neural factors that contribute to neuroticism may be more influenced by experience earlier in life. In support of this notion, a recent study found that early postnatal separations from mother rats daily for three hours caused in pups later in life enhanced reactivity to brief stressors in anxiety behaviors and corticosterone secretion but also in CRH mRNA expression in the Ce (Gillespie & Nemeroff, 2007). The latter implies that early adverse experience may result in a persistent Ce-induced enhanced reactivity via its CRH efferents throughout stress-related neural pathways shown in Figure 24.5, including in the lateral BNST.

3. Peripheral Glucocorticoid System

Peripheral Pathways As shown on the far right side of Figure 24.5, the BNST via CRH efferents activates CRH neurons in the PVN under stressful conditions. CRH is then released from the hypothalamic CRH neurons and is transported via a portal system to the anterior pituitary, where adrenocorticotropic hormone (ACTH) is released into the blood stream, activates the adrenal cortex, which then secretes cortisol (mainly corticosterone in rodents). Cortisol travels through the blood stream and has a diverse set of effects on energy metabolism and neural functioning. In humans and rodents, there are two types of stress-induced cortisol receptors. Type I or mineralocorticoid receptors (MRs) have a high affinity for cortisol and thereby mediate the acute stress-induced effects of cortisol on bodily responses. Type II or glucocorticoid receptors (GRs) have a low affinity for cortisol, and thereby become bound to cortisol only at high levels of cortisol concentration. Such high levels of cortisol in the

hippocampus, acting via GRs, activate inhibitory output from the hippocampus to the hypothalamic CRH secretory neurons, thereby reducing the activity of the CRH-cortisol stress response system. This pathway represents the major negative feedback system for controlling stress-induced CRH-cortisol responses.

Peripheral Glucocorticoid System and Early Adversity Noting that the relations between early adversity and environmental poverty with adulthood health (including stress disorders later in life) appear to be mediated by parental influences, researchers have begun to explore whether these parental influences operate via effects on the development of neural systems that underlie the expression of behavioral and endocrine responses to stress (Gross & Hen, 2004; Meaney, 2001; Sapolsky, 2004). Postnatal handling studies in rats provided early support for this notion. Postnatal handling of 3–15 minutes/day resulted in reduced stress reactivity and fearfulness, and increased exploration; decreased hippocampal aging and more intact cognitive functioning in old age; increased GRs in the hippocampus; and increased GABA A receptors (the activation of which reduces anxiety behavior in rats) in the amygdala, locus coeruleus, and hippocampus. In contrast, maternal separation of rat pups had the opposite effects of postnatal handling. For instance, pups separated from their mothers for 180 minutes/day for 2–14 days (which simulates a scarce environment in which the mother leaves the nest for days at a time to forage for food) show significant increases in CRH mRNA expression in the Ce and PVN; decreased GR mRNA and reduced 5-HT1A responses in the hippocampus; and reduced GR binding in the hippocampus, hypothalamus, and frontal cortex, all of which blunts the CRH negative feedback system. Importantly, these pups also manifested a lifetime hyperresponsivity to unfamiliar stressors.

A series of studies of individual differences in rat maternal behavior toward pups has also supported these findings (Champagne et al., 2008; Leonardo & Hen, 2006; Meaney, 2001; Weaver et al., 2004). Rat mothers naturally differ in their levels of licking/grooming and arched-back nursing (which is less stressful for pups than being compressed by the mother's body during nursing), creating two groups of mothers: high vs low LG-ABN. These different maternal patterns are stable over litters, so they appear to be trait-like under normal conditions. Behaviorally, pups of high LG-ABN mothers show reduced startle responses, increased open-field exploration, and reduced latencies to eat food in a novel environment. Neurobiologically, these pups show reduced plasma ACTH and corticosterone responses to acute stress; increased hippocampal GR mRNA expression and hence increased glucocorticoid negative feedback sensitivity; decreased CRH mRNA levels in the hypothalamus; increased affinity for GABA at its A receptor in the amygdala and locus coeruleus; and an increased 5-HT tone in the hippocampus. Moreover, as pups and adults, offspring of high LG-ABN mothers also show less cell death and increased glutamate receptor levels (resulting in enhanced synaptogenesis) in the hippocampus and enhanced memory on hippocampal-dependent tasks.

Thus, the behavior of the mother toward offspring can apparently program behavioral and endocrine responses to stress that endure the entire life span. Moreover, as illustrated in Figure 24.6, individual differences in stress reactivity mediated by maternal care are transmitted across generations (Gross & Hen 2004). Indeed, though adult mothers must overcome initial neophobia to pups, female offspring of high LG mothers are initially less averse to pups. And when offspring of low LG mothers are raised

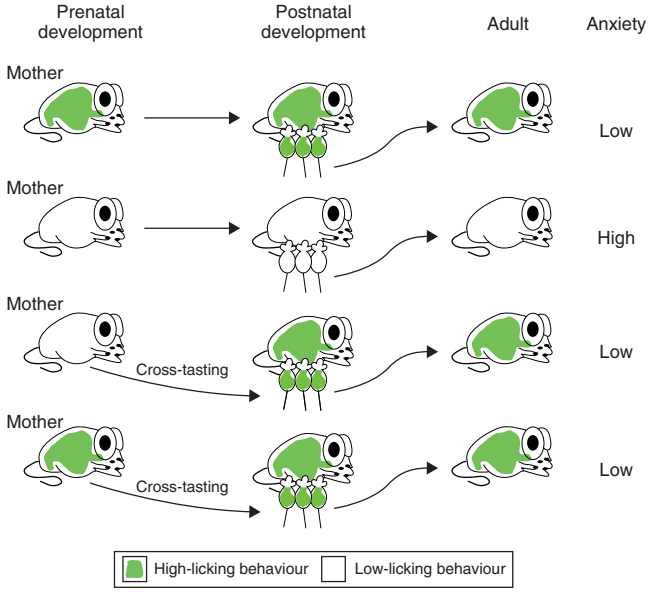


Figure 24.6 Rats raised by mothers that display low licking-and-grooming behavior exhibit more anxiety-related behavior than rats raised by high licking-and-grooming mothers. Cross-fostering studies show that the offspring of low licking-and-grooming mothers raised by high licking-and-grooming mothers are less prone to anxiety-related behavior as adults. This indicates that the effect is mediated by postnatal maternal environment. However, offspring of high licking-and-grooming mothers raised by low licking-and-grooming mothers do not have an increased tendency to develop anxiety-related behavior in adulthood, indicating that specific factors inherited by the high licking-and-grooming offspring protect them from the effects of being mothered by low licking-and-grooming females. See footnote 1. *Source:* Adapted from Gross and Hen (2004).

from birth by high LG mothers (i.e., cross-fostering), these offspring manifest low stress reactivity and anxiety as pups and adults. Importantly, however, although Meaney (2001) reported that raising offspring of high LG mothers with low LG mothers produced stress reactive offspring, this has not been replicated: others have found that these offspring show adult stress phenotypes that are more similar to their high LG biological mother (Figure 24.6; Gross & Hen, 2004). We return to this issue later. But what is clear is that variation in maternal care can affect development of neural systems that mediate stress reactivity, which subsequently influences offsprings' maternal behavior.

It is important to note that there is a convergence between the roles of 5-HT and CRH in these studies that may be significant with respect to the above discussion of the serotonin transporter and CRH in anxiety and stress reactivity. Recall that high LG mothers and their offspring showed increased 5-HT tone in the hippocampus, and that maternal separation reduced 5-HT1A responses in hippocampus.

Stress-induced CRH release onto CRH-R1 receptors in the dorsal raphe nucleus (a major brainstem site of 5-HT neurons) elevates 5-HT concentrations in the hippocampus by 350%. 5-HT activity in the hippocampus activates GR gene expression, providing increased negative feedback to the PVN and Ce CRH neurons. In turn, GR activation enhances postsynaptic effects of 5-HT1A activation, which increases inhibition of excitation in the postsynaptic neuron. Furthermore, 5-HT activation of postsynaptic glutamate neurons in the hippocampus activates Bdnf secretion into the synapse, increasing synaptic processes and decreased aging effects in the hippocampus. Therefore, variation in the functional properties of the 5-HT or the CRH-R1 systems could influence the efficacy of the GR-induced negative feedback system for controlling stress-induced cortisol secretion.

Early Experience and Epigenetic Processes

The critical question concerning the early handling, separation, and maternal care findings is how these influences on stress reactivity and anxiety become long-lasting. Research thus far has supported the role of two mechanisms: epigenetic effects and DNA methylation, both of which involve an alteration of gene expression by experience. In terms of epigenetic effects, as shown in Figure 24.7, DNA is wrapped around proteins called histones, with the DNA and histones collectively comprising chromatin (Tsankova et al., 2007). The functional unit of chromatin is the nucleosome, which is composed of 147 base pairs of DNA wrapped around a core histone group, where there are two copies of each of the four histones (Figure 24.7a). The compactness (openness vs. closedness) of histones in a particular region of chromatin determines how readily transcription factors can access promoters in the DNA (Figure 24.7a). A wide variety of regulators can alter chromatin structure (i.e., its openness), and hence the access to genes. Neurotransmitter (e.g., 5-HT) or hormone (e.g., cortisol) action at receptors can elicit activity in postsynaptic regulators of chromatin structure, and hence access to genes. For instance, activation of MRs and GRs alters the expression of 70–100 genes, 50% of which are upregulated. As we shall see, experience, via neurotransmitter and hormone effects, can permanently alter chromatin regulators and openness to gene transcription, and hence behavior.

Alternatively, in terms of DNA methylation, genes can be stably silenced for substantial periods of time (a lifetime in the case of the second X chromosome in females) when a methyl group is attached to nucleotides in a gene's promotor or exon regions, where the methyl group then tightly binds a repressor protein (Figure 24.7b, Inactive and Repressed sections). Demethylation of a gene leads to enhanced expression of its protein product.

Changes in both chromatin remodeling and DNA methylation state are implicated strongly in the effects of handling and maternal style. Acetylation of histones decreases their binding to DNA (increases chromatin openness), thereby increasing access of transcription factors to promoters and exons. Histones surrounding the GR gene were more acetylated in high LG mothers and their offspring. As illustrated in Figure 24.8, an hypothesized chain of events (Champagne et al., 2008; Sapolsky, 2004; Tsankova et al., 2007) is that high LG rearing results in increased 5-HT neurotransmission in the hippocampus of pups (Point 1 in the figure). The resulting increased 5-HT activation of postsynaptic neurons in the hippocampus leads to strong activation of cAMP, protein kinase A (PKA), and its cascade of events within the postsynaptic neuron. In turn, an increased acetylation of histones and opening of chromatin occurs (Point 2). Also, increased expression of the transcription factor nerve growth factor-inducible protein A (NGFI-A) occurs, which results in increased NFGI-A binding to its binding site located on the first exon of the GR gene (Point 3). Such binding enhances the expression of GRs in the hippocampus, providing enhanced negative feedback effects on central and peripheral CRH release. 5-HT via its postsynaptic effects activates the BDNF gene, which increases synaptogenesis in the hippocampus when released into the synaptic cleft (Point 5).

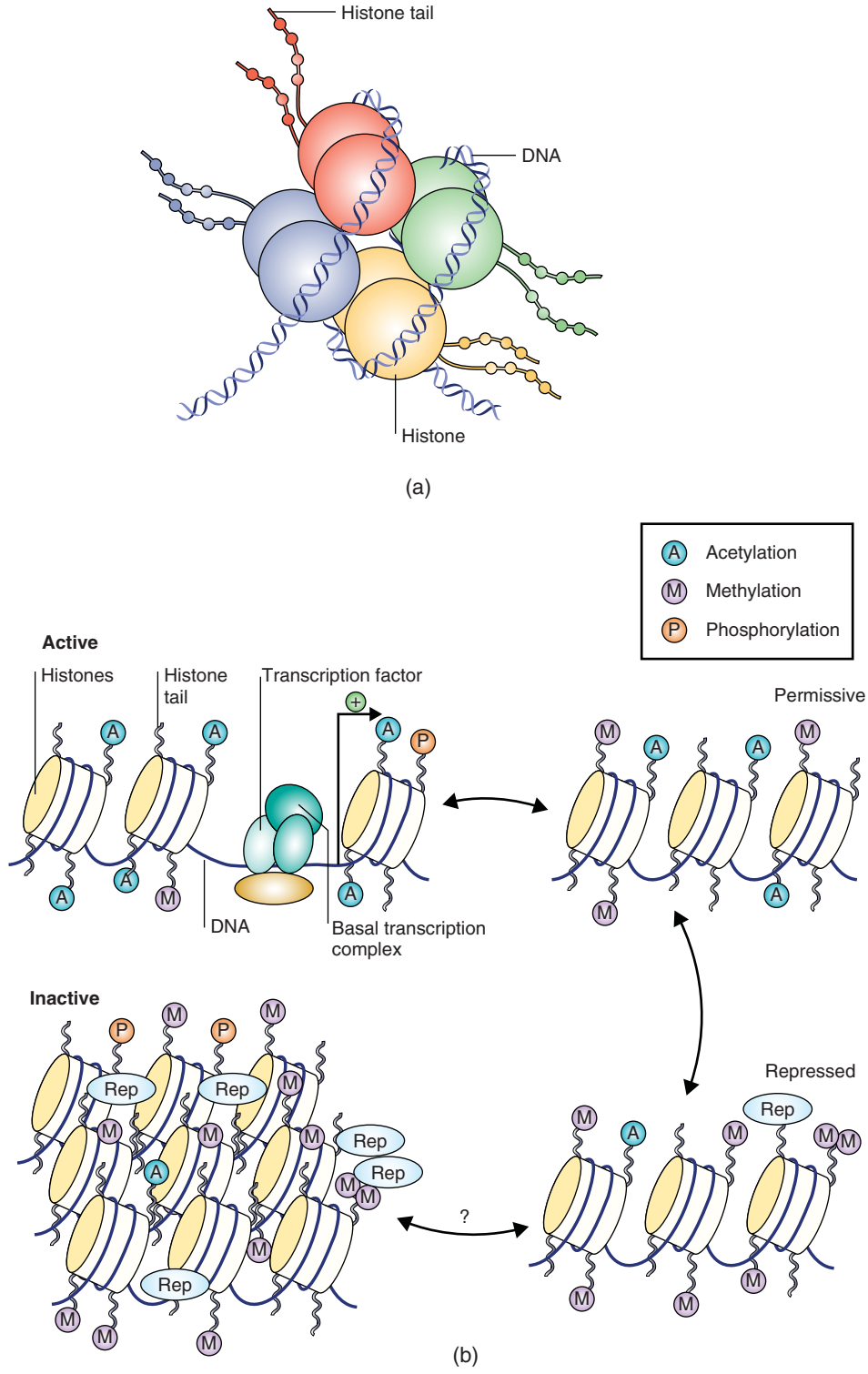


Figure 24.7 General scheme of chromatin remodeling. a) Picture of a nucleosome showing a DNA strand wrapped around a histone octamer composed of two copies each of the histones. b) Chromatin can be conceptualized as existing in two primary structural states: as active or open (top left) in which histone acetylation (a) is associated with opening the nucleosome to allow binding of the basal transcriptional complex and other activators of transcription; or as condensed or closed where all gene activity is permanently silenced (bottom left). In reality, chromatin exists in a continuum of several functional states (active; permissive (top right); repressed (bottom right; and inactive). See footnote 1. *Source:* Adapted from Tsankova et al., 2007.

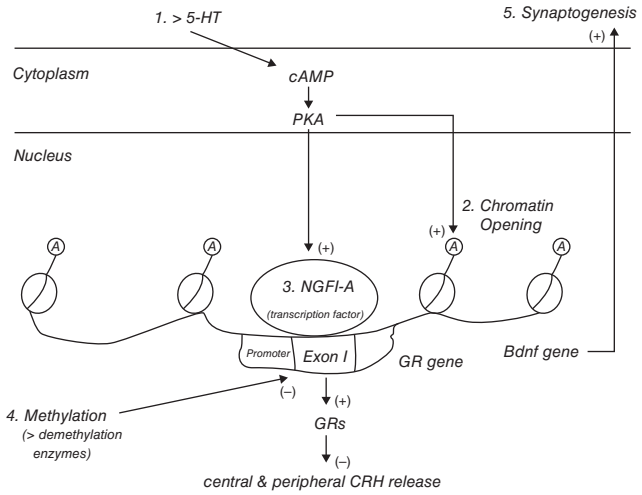


Figure 24.8 Five effects of high LG maternal care in the hippocampus on gene expression.

In terms of DNA methylation, it has been found that the methylation state of the NGFI-A binding site on the first exon of the GR gene is plastic around the time of birth. The site is then methylated the first day after birth, decreasing transcription of the hippocampal GR gene. Over the next week, exposure to high LG mothering (by biological or cross-fostering females) caused the binding site to be demethylated, increasing transcription of the GR gene and hence hippocampal GRs (Point 4). Recent evidence supports a causative role for the above histone actylation and methylation effects. A pharmacological inhibitor of histone deacetylation opens up chromatin and facilitates access of demethylating enzymes, shifting the balance in chromatin toward acetylation. Administration of this inhibitor to adult rats raised in a low LG environment transformed them into a high LG adult in terms of stress reactivity. This behavioral effect was accompanied by an increase in NGFI-A access to the now demethylated promotor and exon 1 of the GR gene, and by reduced levels of circulating glucocorticoids.

Significantly, most of the effects of handling and maternal style occur only within a critical developmental period (Champagne et al., 2008; Gross & Hen, 2004; Leonardo & Hen, 2006; Meaney, 2001). Handling, maternal style, and methylation status all must be present in the first week of life to have an effect in rodents. This is consistent with the findings discussed above, where the first three weeks in rodents are critical in the developmental effects of 5-HT, the effects of knocking out 5-HT1A receptors and MAOA, and in CRH reactivity. Similarly, SSRIs (which result in enhanced 5-HT availability) administered during weeks 1–3 (but not during weeks 6–8) normalize the glucocorticoid response in parentally stressed mice, indicating that this critical developmental period may have a relatively narrow window. Thus, as summarized in Figure 24.9, experience during early postnatal weeks in rodents, and perhaps early months in primates, appear to interact with genetic polymorphisms in 5-HT, Bdnf, and MAOA functioning, creating a critical period for establishing effective synaptic development in the forebrain structures that mediate anxiety in response to experience-dependent signals.

Extraversion

Dopamine Contributions to Extraversion. Through empirical studies and integrative reviews, we have demonstrated that extraversion reflects the activity of a mammalian

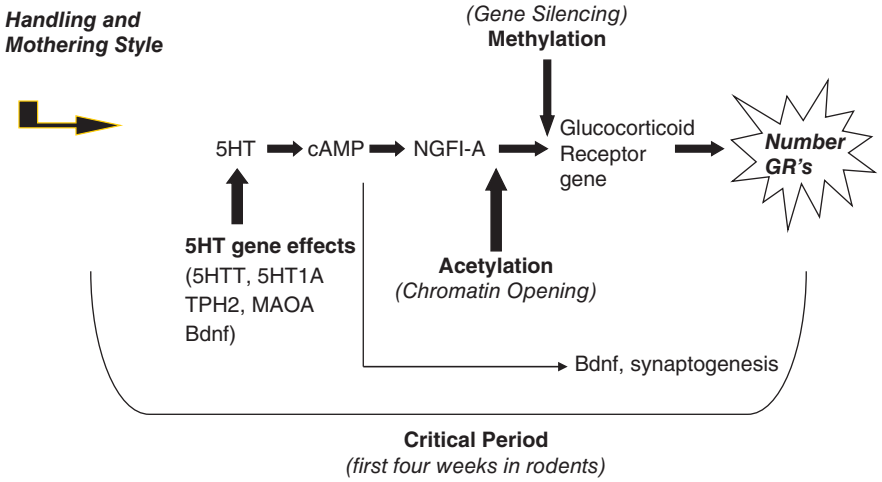


Figure 24.9 A summary of the effects of maternal experience and genetic polymorphisms on gene expression of glucocorticoid receptors during an early postnatal period. See footnote 1.

behavioral approach system based on positive incentive motivation (Depue, 2006; Depue & Collins, 1999; Depue & Morrone-Strupinsky, 2005). This system is activated by, and serves to bring an animal in contact with, unconditioned and conditioned rewarding incentive stimuli. Incentives are inherently evaluated as positive in valence, and activate incentive motivation, increased energy through sympathetic nervous system activity, and forward locomotion as a means of bringing individuals into close proximity to rewards. The incentive state is clearly evident in the phenotypic features of extraversion, and is associated with subjective feelings of desire, wanting, excitement, elation, enthusiasm, potency, and self-efficacy that are distinct from, but typically co-occur with, feelings of pleasure and liking.

Animal research demonstrates that the positive incentive motivation and experience of reward that underlies a behavioral system of approach is dependent on the functional properties of the midbrain ventral tegmental area (VTA) dopamine (DA) projection system. DA agonists or antagonists in the VTA or nucleus accumbens (NAS), which is a major terminal site of VTA DA projections, in rats and monkeys facilitate or markedly impair, respectively, a broad array of incentive motivated behaviors. Furthermore, dose-dependent DA receptor activation in the VTA-NAS pathway facilitates the acute rewarding effects of stimulants, and the NAS is a particularly strong site for intracranial self-administration of DA agonists. DA agonists injected in the NAS also modulate behavioral responses to *conditioned* incentive stimuli in a dose-dependent fashion. In single-unit recording studies, VTA DA neurons are activated preferentially by appetitive incentive stimuli, and DA cells, most numerously in the VTA, respond vigorously to and in proportion to the magnitude of both conditioned and unconditioned incentive stimuli and in anticipation of reward (Schultz, 2007). Similarly, in human neuroimaging studies, increased activation in the VTA and NAS correlates with the amount of reward anticipated, and with ratings of excitement preceding the reward (Canli, 2006; Knutson & Bhanji, 2006). Morevover, during acute administration the intensity of a subject's subjective euphoria increased in a dose-dependent manner in proportion to cocaine binding to the DA uptake transporter (and hence to DA levels) in the striatum (Drevets et al., 2001; Volkow et al., 1997). Hence, taken together, the animal and human evidence demonstrates that the VTA DA–NAS pathway is a primary neural circuit for incentive motivation and its accompanying subjective state of reward.

Consistent with these findings are results with a polymorphism of the dopamine D4 receptor gene on chromosome 11 (Munafo et al., 2003). The D4 receptor is part of the D2 family of DA receptors, which are generally inhibitory in nature. The D4 polymorphism is characterized by variation in the number of repeats of a 48-base-pair unit in exon 3. The most common repeats in the population are 4 and 7 repeats, where the 7-repeat allele is characterized by a two-fold reduction in inhibitory effects on postsynaptic second messenger cAMP relative to the 4-repeat allele. Several small studies have found the 7-repeat allele to be associated with increased extraversion levels relative to the 4-repeat allele, and this was also found using behavioral features of positive emotion in a study of 8–12 month old infants (Lakatos et al., 2003). When this polymorphism is taken in interaction with a polymorphism of the DA transporter (DAT) (one allele being associated with reduced DA uptake and hence increased time of DA in the synapse to activate postsynaptic receptors), impulsivity was significantly increased in terms of number of comission errors in a go/no-go task.

In the discussion above of a threshold model of behavioral responding, it was argued that higher levels of neurobiological traits underlying personality would enhance the association of neutral cues with emotional state. We found that high extraverts more readily associate specific and general contextual cues to DA-agonist induced subjective reward than low extraverts, who showed no associative conditioning at the dose level of methylphenidate used in the studies (Depue, 2006). These findings are consistent with an enhanced reward encoding of positive cues, and are consistent with the fact that extraversion is correlated with increased amygdala activation to happy versus neutral and negative faces. Moreover, the latter finding implies early detection of the enhanced weighted positive stimuli in the amygdala, which through back-projections to many areas of the brain, including sensory processing regions, can bias perceptual processing and attention to positive cues in the environment. Several studies support just such a bias in extraversion (Canli, 2006).

Early Adversity and Dopamine Functioning Early adverse experience in animals has a marked effect on DA functioning, as summarized in Figure 24.10. Single intense stressors or repeated, prolonged stressors, including maternal separations in neonatal rats and monkeys, lead to a sensitization of NAS DA release to repetition of the same stressor or to novel stressors and DA-agonists later in life (Point 6 in the figure; Depue & Collins, 1999; Meaney et al., 2002). There is also an increase in the acquisition of self-administration, and a reduced threshold in terms of

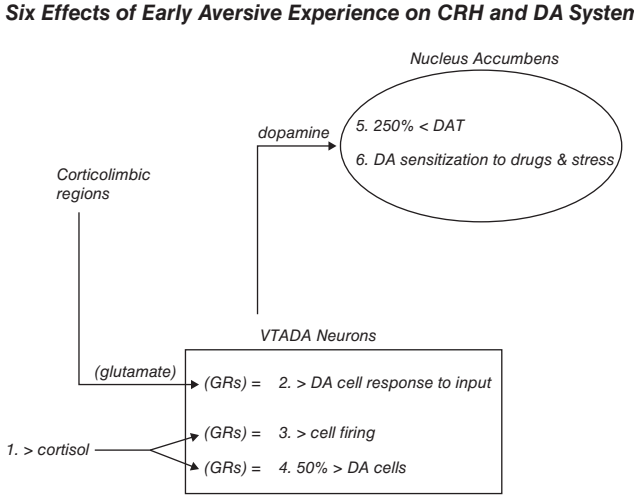


Figure 24.10 Six effects of early aversive experience on glucocorticoid and DA systems in the VTA and NAS.

effective dosage of psychostimulants, alcohol, and opiates, and an increased intensity of effort (craving?) to obtain these drugs (Meaney et al., 2002). Furthermore, rat pups exposed to maternal separations have a 250% reduction in DA transporters in the NAS as adults, which increases time of DA availability at postsynaptic receptors, whereas rats with a history of handling show reduced DA release in the NAS to stress and DA-agonist drugs (Point 5; Meaney et al., 2002).

These effects appear to be enhanced by an interaction of glucocorticoid activation of GRs with DA. Amphetamine and stress both increase corticosterone secretion and NAS DA release. Administration of dexamethasone (synthetic cortisol) prenatally and during the first seven postnatal days in rats results in a 50% increase in VTA DA neurons (Point 4), and increased corticosterone and NAS DA release to stress and DA-agonist drugs in adulthood (McArthur et al., 2005). Even adult humans who report poor maternal care as children have stress-induced increased cortisol levels that correlate ($r = 0.78$) with increased NAS DA release (Pruessner et al., 2004). This effect is enhanced by stressor-induced prolonged oversecretion of cortisol (Point 1) that activates GRs located on VTA DA neurons (Oswald et al., 2005). Such activation has the effect of increasing DA cell responses to input from corticolimbic regions (Point 2), possibly from an enhancement of glutamate release mediated by GRs on glutamate terminals that synapse on VTA DA neurons. In addition, cortisol activation of GRs on VTA DA neurons also enhances the frequency of DA cell firing (Point 3).

Thus, prolonged stressors, such as poor, conflictual, violent, or inconsistent familial environments or physical or sexual abuse early in life, can sensitize the VTA-NAS DA system in an enduring manner. This may have significance for personality disturbance. High levels of extraversion are often associated with histrionic-impulsive behavioral features that can lead to both occupational and interpersonal impairment. In addition, if *extreme* levels of extraversion reflect a sensitized DA system due to early adverse conditions, the risk for increased acquisition of addiction to even low doses of DA-agonist drugs (psychostimulants, alcohol and opiates) later in life may be significantly increased. Also, the increased associative conditioning of context to reward found in high extraverts by us may contribute to rapid conditioning of drug-associated contexts that enhance drug craving and maintenance of addiction. All of these effects would aggravate personality disturbance that is created in combination with other subsets of critical traits, such as neuroticism.

Social Closeness/Agreeableness

In contrast to the highly motivating incentive state associated with extraversion, the core content of social closeness and agreeableness scales reflects the operation of neural processes that create a warm, affectionate, gratifying subjective emotional state elicited by affiliative stimuli, such as soft touch (kissing, caressing, stroking, play); sexual touch; hair grooming; psychological and physical warmth; a caring, smiling, friendly face; soft, caring vocalizations; and shared intimacy (symbolic touching). Our hypothesis is that the subjective emotional experience of warmth and affection reflects the *capacity to experience consummatory* ***reward*** *that is elicited by a broad array of affiliative stimuli* (Depue & Morrone-Strupinsky, 2005). This reward capacity is viewed as providing the key element utilized in associative conditioning processes that permit the development and maintenance of longer-term affective bonds that are characteristic of social organization in human and other primate societies.

A broad range of evidence suggests a role for the endogenous opiate neuropeptide in reward that is exerted by opiate neurons in the hypothalamic arcuate nucleus that project to many brain regions. Most relevant to affiliative reward is the mu (μ) opiate receptor (OR) family, which is the main site of exogenously administered opiate drugs (e.g., morphine) and of endogenous endorphins (particularly, *B*-endorphin) (Depue & Morrone-Strupinsky, 2005). Rewarding properties of μOR agonists are directly indicated by the fact that animals will work for the prototypical μ-agonists morphine and heroin, and that they are dose-dependently self-administered in animals

and humans. *B*-endorphin release on μOR receptors is increased in rats, monkeys, and humans by lactation and nursing, sexual activity, vaginocervical stimulation, maternal social interaction, brief social isolation, and grooming and other nonsexual tactile stimulation (Depue & Morrone-Strupinsky, 2005).

In monkeys and rodents, social bonding is not possible without soft tactile stimulation from the mother (Fleming et al., 1994), and this may involve activation of the μ-opiate system. Mammals, and especially primates, have evolved particular receptors on the skin and a sensory pathway for soft touch (Liu et al., 2007; Olausson et al., 2002) that projects to the anterior insular cortex, a structure that mediates awareness of the subjective experience of emotions (Craig 2009). Via projections to the rostral ACC, the anterior insula can activate *B*-endorphin neurons in the arcuate nucleus which activate reward and physiological quiescence via projections to the VTA-NAS and brainstem regions.

The rewarding effect of opiates may be especially mediated by μORs located in the NAS and VTA, both of which support self-administration of μOR agonists that is attenuated by intracranially administered μOR antagonists. Destruction of DA terminals in the NAS also showed that opiate self-administration is independent of DA function, at least at the level of the NAS (Laviolette et al., 2004). Rewarding effects of opiates are also directly indicated by the fact that a range of μOR agonists, when injected intracerebroventricularly or directly into the NAS, serve as unconditioned rewarding stimuli in a dose-dependent manner in producing a conditioned place preference, a behavioral measure of reward. VTA-localized μORs particularly in the rostral zone of the VTA mediate (1) rewarding effects such as self-administration behavior and conditioned place preference; (2) increased sexual activity and maternal behaviors; and (3) the persistently increased play behavior, social grooming, and social approach of rats subjected to morphine in utero. Transgenic mice lacking the μOR gene show no morphine-induced place preferences nor physical dependence from morphine consumption. And significantly, opiate but not oxytocin antagonists block the development of partner preference that is induced specifically by *repeated* exposure and *repeated* sexual activity in rodents (Carter et al., 1997).

Individual differences in social closeness are subject to strong genetic influence (Tellegen et al., 1988). If personality disturbance occurs in the region located at the extreme tails of individual difference distributions in the trait of social closeness, it is important to show that the neuromodulators associated with the trait are sources of individual differences in these behavioral systems. Individual differences in humans and rodents have been demonstrated in levels of μOR expression and binding that are associated with a preference for uOR-agonists such as morphine (Uhl et al., 1999; Zubieta et al., 2001). In humans, individual differences in CNS μOR densities show a range of up to 75% between lower and upper thirds of the distribution (Uhl et al., 1999), differences that appear to be related to variation in the rewarding effects of alcohol in humans and rodents.

One source of this individual variation is different single nucleotide polymorphisms (SNPs) in the μOR gene, OPRM1 (Bond et al., 1998; Gelernter et al., 1999). The most prevalent of these is A118G, with an allelic frequency of ~10%. This SNP bound *B*-endorphin three times more tightly than the most common allelic form of the receptor. Furthermore, *B*-endorphin is three times more effective in agonist-induced activation of G-protein–coupled potassium channels at the A118G variant receptor compared with the most common allelic form. Importantly, this genetic variation in μOR properties is related to response to rewarding drugs, such as morphine, alcohol, and cocaine, and to opiate self-administration behavior in animals (Zhang et al., 2007). Taken together, these studies suggest that genetic variation in μOR properties in humans and rodents is (1) substantial; (2) an essential element in the variation in the rewarding value of opiate agonists; and (3) critical in accounting for variation in the Pavlovian learning that underlies the association between contextual cues and reward, as occurs in partner and place preferences (Van den Oever et al., 2008).

Two recent studies have found that μORs are critical in modulating the strength of attachment behaviors in animals. Transgenic mice lacking the μOR gene showed markedly *reduced* (1) opiate self-administration reward; (2) acquisition of place and mate/pup preferences; (3) maternal behaviors (pup tactile stimulation, pup retrieval, nursing); (4) play and social grooming; and (5) NAS DA release to ethanol and amphetamine (Moles et al., 2004). Also, juvenile monkeys having the homolog of the μOR gene polymorphism that is characterized by enhanced *B*-endorphin functioning showed greatly enhanced distress and a lack of attachment behavior as a function of a series of maternal separations (Barr et al., 2008). And, finally, we have shown that a μOR antagonist in subjects with high trait levels of social closeness *reversed* their heightened ratings of affection to film scenes and their greater tolerance to heat (mediated by μORs) such that they now expressed levels not different from low trait social closeness subjects (Depue, 2006).

In terms of effects of experience on social closeness, it is the only higher order trait that shows significant within-family experience effects (Tellegen et al., 1988), indicating that both familial and nonfamilial relationships have a marked effect on trait levels. Of course, there is an immense animal and human literature that demonstrates that level of attachment is affected by interpersonal experience starting in the postnatal period (Fleming et al., 1999). Unfortunately, no studies of experience-dependent modulations of the μOR system have been reported, so it is unclear whether experience operates on social bonding via this system. There is emerging evidence, however, that social interactions during the neonatal period organize the subsequent expression of affiliative behavior by altering sensitivity to neuropeptides (Cushing & Kramer, 2005). What is clear is that low trait levels of social closeness/agreeableness accompany neuroticism as being the strongest personality associates of a range of personality disturbances. Whether these low trait levels are due to adverse early experience or an interaction of genetic and experiential factors needs empirical attention.

Social Rejection Sensitivity

Items covering the nature of social rejection sensitivity (SRS) have not been included in personality questionnaires. We view this as a serious oversight, since close interpersonal relationships are modulated by at least two very strong emotional systems: social closeness and bonding, drawing people together, and SRS, which either pulls people closer to avoid separation anxiety or pushes people away. SRS is also a central feature in personality disturbance, appearing in classical PD categories as borderline, dependent, and avoidant.

SRS is elicited by social separation due to group exclusion and whenever social relationships are threatened, damaged, or lost. It is also elicited by more symbolic forms of withdrawal of love or acceptance, including negative feedback about the self; verbal devaluation; disapproving, frowning faces; averted gazes; and expressions of the social emotions of contempt, indignation, and disgust by others. In response, people experience hurt, pain, anxiety and agitation, sadness, and the social emotions of guilt, shame, and embarrassment. Such a neurobehavioral system allows others to control social transgressions, and the rejected person avoids social ostracization that would follow if no anxiety or guilt were experienced—which in monkeys leads to death within weeks. From an evolutionary standpoint, SRS may have developed to maintain closeness of long-developing toddlers to nourishment- and safety-providing caregivers (Eisenberger & Lieberman 2004). Thus, SRS may be based on social pain—the distressing experience arising from the perception or potential psychological distance from close others or a social group (Eisenberger & Lieberman, 2004).

The description of the distress associated with social rejection is dominated by the terms pain and hurt, terms that are not ordinarily associated with other negative emotions. Physical pain has two components: physical sensory experience, and affective experience of unpleasantness and psychological pain and hurt. The latter component is associated with activation in the dorsal region of the ACC (dACC). This region is also the location of neurons that provide an aversive, punishment signal to the basolateral amygdala, where that aversive signal is paired with neutral cues in emotional associative learning (Johansen & Fields 2004). Thus, the dACC may provide the foundation for affectively aversive signals during the experience of harm—either physical harm or social harm. Indeed, recent studies have found that during the experience of social rejection, humans show intense activation of the dACC, which presumably activates the amygdala to generate the bodily responses that create the unpleasant emotional experience (Eisenberger & Lieberman, 2004; Somerville et al., 2006).

Though we are not aware of any research on the effects of experience on SRS levels or dACC activation levels, it is clear that familial and nonfamilial experiences of social rejection affect social trust and security of attachments. The entire area of SRS is understudied in psychology and neuroscience.

Constraint/Conscientiousness

The Nature of Constraint

Constraint represents a broad trait of impulsivity that modulates the expression of many domains of behavior, including emotional, motor, cognitive, and sensory reactivity (Carver, 2006; Depue & Collins, 1999; Depue & Lenzenweger, 2005; Depue & Spoont, 1986; Spoont, 1992; Zald & Depue, 2001). Whereas the four traits described above all reflect the activity of neurobehavioral systems, constraint lacks ties to any specific motivational-emotional system (Carver, 2006; Depue & Collins, 1999; Spoont, 1992). Thus, we have proposed that constraint is the personality trait that reflects the greatest CNS weight on the construct of a minimum response threshold (Depue & Collins 19999; Depue & Lenzenweger, 2005; Depue & Spoont, 1986). This can be visualized in Figure 24.2, where the trait of constraint would be the major modulator of the

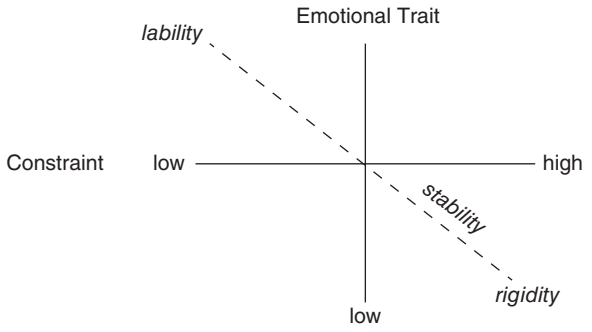


Figure 24.11 The interaction of an emotional trait with the higher order trait of constraint, forming a diagonal of behavioral stability extending from labile to rigid.

threshold for behavioral manifestation. In this model, emotional higher order personality traits reflect the influence of neurobiological variables that strongly contribute to the threshold for responding, such as DA in the facilitation of incentive motivated behavior, μ-opiates in the experience of affiliative reward, and CRH in the potentiation of anxiety. Constraint modulates the probability of elicitation of all of those variables.

Significantly, as shown in Figure 24.11, constraint in its modulatory interaction with an emotional personality trait creates a diagonal of stability of emotional behavior. This diagonal extends from lability where the emotional trait's level is high and constraint is low (i.e., increasingly easy stimulus elicitation of behavior due to a low threshold created by the interaction as in Figure 24.2) to rigidity when the emotional trait's level is low and constraint is high (i.e., increasingly difficult stimulus elicitation of behavior due to a high threshold created by the interaction).

Constraint and Serotonin Functioning

Functional levels of neurotransmitters that provide a strong, relatively generalized *tonic inhibitory* influence on behavioral responding would be good candidates as significant modulators of a response elicitation threshold, and hence would likely account for a large proportion of the variance in the trait of constraint. We and others previously (Carver, 2006; Coccaro & Siever, 1991; Depue, 1995; Depue & Spoont, 1986; Lesch & Canli, 2006; Panksepp, 1998; Spoont, 1992; Zald & Depue, 2001; Zuckerman 1994) suggested that 5-HT, acting at multiple receptor sites in most brain regions, is such a modulator. 5-HT modulates a diverse set of functions—including emotion, motivation, motor, affiliation, cognition, food intake, sleep, sexual activity, and sensory reactivity (Carver, 2006; Depue & Spoont, 1986; Lesch & Canli, 2006; Spoont, 1992). Furthermore, *reduced* 5-HT functioning in animals (Depue & Spoont, 1986; Spoont, 1992) and humans (Coccaro & Siever, 1991) is also accompanied by *irritability* and *hypersensitivity* to stimulation in most sensory modalities (Spoont, 1992). Thus, 5-HT plays a substantial modulatory role in general neurobiological functioning that affects many forms of motivated behavior. In this sense, constraint might be viewed as reflecting the influence of the CNS variable of 5-HT, which we refer to as *neural constraint* in Figure 24.11. In support of this notion, we found that 5-HT agonist-induced increases in serum prolactin secretion were correlated significantly and specifically only with the Constraint/Impulsivity (control) scale (-0.44, $p < .01$) from Tellegen's personality questionnaire of 13 primary scales (Depue, 1995).

Constraint, Instability, and Personality Disturbance

Along with neuroticism and low social closeness, constraint is well correlated with personality disturbance, particularly of the type related to unstable behavior (as in the classical unstable group of PDs of histrionic, antisocial, and borderline). A vast body of animal and human evidence consistently associates *reduced* functioning of 5-HT neurotransmission with *behavioral instability*. In addition, recent research on two polymorphisms of the gene for tryptophan hydroxylase (TPH2, which is localized in brain rather than the periphery), the rate limiting enzyme in the synthesis of 5-HT, indicates marked behavioral instability (particularly in affective aggression and impulsive suicide) and increased amygdala reactivity to positive and negative emotional slides in any one of the alleles that reduces brain 5-HT by 50% (Hennig et al., 2005; Manuck et al., 1999; Rujescu et al., 2002). Furthermore, reduced levels of 5-HT are associated with many clinical conditions, including impulsive, violent suicide across several types of disorder, obsessive-compulsive disorder, disorders of impulse control, aggression and irritability, depression, anxiety and enhanced stress reactivity, arson, unconstrained sexual behavior, and substance abuse (Carver, 2006; Coccaro & Siever, 1991; Depue & Spoont, 1986; Winstanley, 2005).

The nature of this instability depends on the neurobehavioral system being elicited. An example of the interaction of neurobiological variables associated with constraint (5-HT) and extraversion (DA) helps to illustrate this point (see Depue & Lenzenweger, 2005, for a discussion of the behavioral consequences of an interaction of each of the higher order traits with constraint). 5-HT is an inhibitory modulator of a host of DA-facilitated behaviors, including the reinforcing properties of psychostimulants, novelty-induced locomotor activity, the acquisition of self-administration of cocaine, and DA

utilization in the NAS (Depue & Collins, 1999; Depue & Spoont, 1986; Spoont, 1992). This modulatory influence arises in large part from the dense dorsal raphe 5-HT efferents to the VTA and NAS, connections that are known to modulate DA activity (Spoont 1992). A 5-HT–related reduction in the threshold of DA facilitation of behavior results in an exaggerated response to incentive stimuli, which is most apparent in reward–punishment conflict situations. In such situations, exaggerated responding to incentives results in (1) a greater weighting of immediate versus delayed future rewards; (2) increased reactivity to the reward of safety or relief associated with active avoidance (e.g., suicidal behavior); (3) impulsive behavior, i.e., a propensity to respond to reward when withholding or delaying a response may produce a more favorable long-term outcome; and (4) various attempts to experience the increased magnitude and frequency of incentive reward (e.g., self-administration of DA-active substances; Coccaro & Siever, 1991; Depue & Iacono, 1989; Lesch & Canli, 2006; Winstanley et al., 2005). All of these effects impair the ability to sustain long-term goal-directed behavior programs (such as obtaining a college degree) by mental representations of expected rewards that can be repeatedly accessed, held online in prefrontal cortex, and thereby symbolically motivate behavior (Depue & Collins, 1999).

This discussion suggests an important role for 5-HT in the model of personality disturbance shown in Figure 24.1. Reduced levels of 5-HT create a highly reactive individual in terms of hyperactivity of the ANS to stress, hyperirritability to sensory overload and life frustrations, enhanced affective aggression to even minor provocations, unplanned suicidal attempts when stressors become unbearable, instability of attachment to others (vacillating between approach and avoidance), and labile positive and anxious moods. This behavioral instability may reflect the effect of 5-HT's reduced neural constraint over many CNS variables (Spoont, 1992), which might explain how alterations of 5-HT functioning are found in so many different clinical disorders. Such weak constraint over CNS variables might render the effects of stress as markedly increased on biology and hence behavior. In other words, 5-HT–constraint may serve as a general modulator of expression on the reaction surface, increasing expression of personality disturbance during times of life stress and interpersonal chaos. At the same time, stress may increase the probability that 5-HT constraint will disinhibit the elicitation of the neurobehavioral systems of other emotional traits: animal research has shown that stressors of many types, but especially perceived or actual social aggression and social isolation (both of which are common in the life of individuals with personality disturbance), further decrease 5-HT functioning. Thus, 5-HT constraint may serve as a strong modulator of the extremity of an individual's position on a trait and, in turn, the *course* of intensity of personality disturbance over the life span.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

The above discussion has suggested a number of variables that contribute to the development of a position within the reaction surface (gray area in Figure 24.1) of personality disturbance. In our view, the sine qua non of being within that reaction surface, being susceptible to personality disturbance, is extremity on the neurobiological variables underlying a critical subset of emotional traits. The reason for this is that being at the extreme has marked effects on the threshold for eliciting those traits under stimulus conditions. Depending on the phenotypic features of personality disturbance (which is dependent not just on extremity but on the subset of interacting major traits, as outlined in Figure 24.1), the *impairing* threshold value may be *low*, as in the case of neuroticism, social rejection sensitivity, affective aggression, fear, and extraversion (in terms of histrionic, impulsive behavior), or *high*, as in the case of affiliative bonding and extraversion (in terms of depressive behavior). As noted in the discussion of Figure 24.2, extreme threshold values lead to variation in the range of stimuli that are subject to negative or positive associative conditioning and to subsequent biasing of perceptual and attentional processes to stimuli that elicit a certain trait. Both of these latter effects likely help to maintain and increase the extremity of trait values over time.

A second important contributor to being within the reaction surface is the functioning of 5-HT, which as shown in Figure 24.2 modulates the value of the threshold required for trait elicitation. As shown in Figure 24.11, especially *reduced* functioning of 5-HT creates instability when interacting with extreme levels of an emotional trait. It is important to note that 5-HT–induced instability is manifested at two different levels: (1) at the phenotypic level as in Figure 24.11; but also (2) at the neurobiological level. Recall the discussion of 5-HT x DA interactions: reduced 5-HT functioning in the NAS results in a very low threshold for eliciting DA facilitation of behavior by incentive stimuli. *This illustrates that the impact of environmental stimulation on neurobiological variables underlying emotional traits is modulated by 5-HT functioning*.

Both the extremity of neurobiological variables underlying emotional traits and 5-HT functioning are modified by genetic polymorphisms, with substantial effects noted so far for the genes of the DAD4 receptor, DAT, the μOR, MAOA, Bdnf, 5-HTT, 5-HT1A receptor, and TPH2. Thus, genetic contributions to position within the reaction surface are likely to be significant.

There is a growing literature that indicates that stressful environmental experiences have a robust effect on the functioning of neurobiological variables underlying personality traits. The stressors may derive from environmental conditions that are external (e.g., poverty, dangerous neighborhoods), within the family (e.g., conflict, violence, sexual abuse, caregiver separation or neglect), or within the caregiver (e.g., maternal style). The exciting aspect of this area of research is the beginning of an understanding of how these environmental influences affect neurobiological functioning and hence behavioral variation in enduring ways. This was discussed in terms of sensitization in extraversion, and a variety of other epigenetic effects in neuroticism. Thus, this raises the possibility that environmental history may strongly affect an individual's extremity on critical personality traits, and hence position within the reaction surface of personality disturbance.

Both genetic and environmental stress variables appear to be most profound and enduring when they exert their effects during early developmental periods. This may be due to the fact that brain development has critical developmental windows in postnatal, childhood, and adolescent periods. Thus, the s-allele, other genetic variations in 5-HT functioning, and MAOA activity have substantial effects on the development of neural circuitry in the postnatal period when the forebrain is undergoing exuberant experience-expectant dendritic and axonal growth. These early effects endure life long, but are not significant when introduced in adulthood. There are other periods of experience-expectant brain growth in childhood, and robust growth in cortico–cortical connections between prefrontal and posterior regions in adolescence (Blakemore 2008). It is perhaps for this reason that the well-documented stability of most higher order personality traits is valid mainly *after* adolescence.

The Role of Individual Differences in the Interaction of Genes and Environment

In consideration of these genetic and environmental effects, the role of individual differences in trait neurobiological functioning is often neglected. However, as indicated in the discussion of Figure 24.2, the effects of experience on neural functioning are dependent on preexisting trait levels of genetically influenced neural functioning. This dependency has been demonstrated recently several times (Caspi et al., 2002, 2003), but the influence of individual differences is often neglected in discussions of the effects of experience on neural systems (e.g., Meaney, 2001). A dramatic example of this dependency is illustrated in Figure 24.12, which is based on a body of research with rats who differ in DA functioning in the NAS, the site of DA's facilitation of incentive reward (Depue & Collins 1999). In this example, the stimulus is not environmental but rather a direct activation of DA receptors by amphetamine (a DA agonist), and its effect on the acquisition of self-administration of amphetamine is plotted in two groups of rats differing markedly in trait DA functioning. Whereas the high DA group readily acquires self-administration behavior, the low DA group is unaffected by the stimulus (amphetamine). Apparently the amphetamine has too weak an effect on the rats with low DA reactivity to reach the threshold of experiencing a subjective sense of reward. Thus, these two groups of rats will encode their surrounding context in opposite ways (as rewarding vs. neutral), such that the subsequent efficacy of the context will only be enhanced for the high DA group. These findings also mean that stress-induced epigenetic effects on the DA system (e.g., sensitization) will be much greater in the high versus low DA group. One can imagine dramatic differences in the developmental trajectories of these two groups in terms of (1) the elaborateness of their associative networks of positive emotional

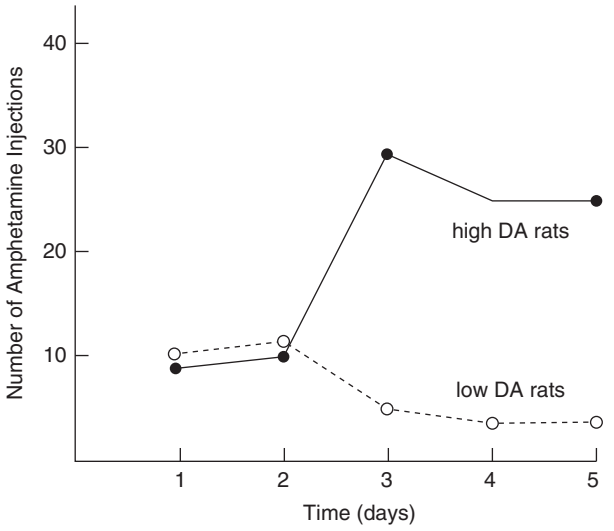


Figure 24.12 Rats differing in dopamine (DA) functioning show a different course of acquisition of self-administration of amphetamine over days.

environmental contexts; and (2) the capacity of these contexts to elicit epigenetic effects and (positive incentive motivated behavior.

The same point can be made from the findings illustrated in the last two rows of Figure 24.6. The cross-fostered offspring of low LG mothers raised by high LG mothers are less prone to anxiety-related behavior as adults. This indicates that the effect is mediated by postnatal maternal environment. However, offspring of high LG mothers raised by low LG mothers do not have an increased tendency to develop anxiety-related behavior in adulthood, indicating that specific factors inherited by the high LG offspring modify or protect them from the effects of being mothered by low LG females.

Similarly, from the results in Figure 24.13, it was concluded that the genotypic variation in MAOA activity was only expressed as significant antisocial behavior with experience of severe childhood maltreatment: the genotype's effects on behavior are dependent on level of environmental adversity. An alternative perspective suggests that, since there is a dimension of childhood maltreatment from none to severe and the level of antisocial behavior is correlated with that dimension, the extent of environmental influence on antisocial behavior is dependent on genetically influenced neurobiological trait levels (i.e., those created by variation in MAOA activity levels)—once environmental adversity rises above none.

Both MAOA groups show increasing behavioral responses to increasing stress; it is just that stress activates

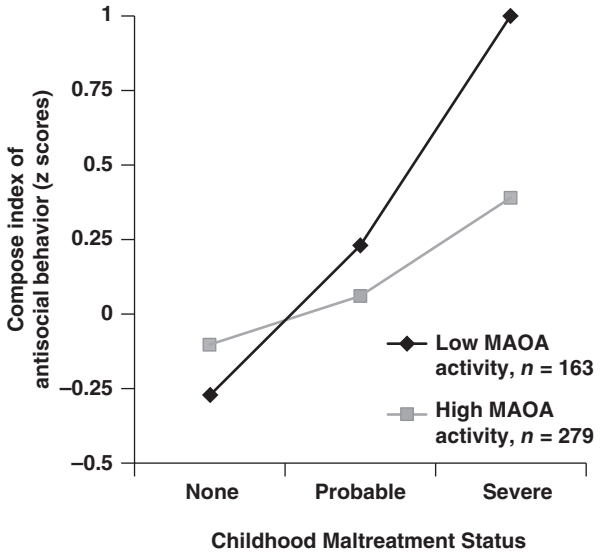


Figure 24.13 Effects of increasing levels of childhood maltreatment on antisocial behavior as a function of a genetic polymorphism in MAOA. *Source:* Adapted from Caspi et al. (2002).

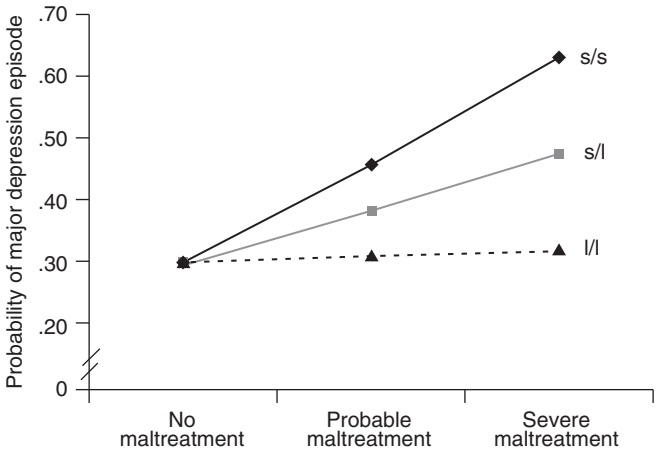


Figure 24.14 Effects of increasing levels of childhood maltreatment on depression as a function of a genetic polymorphism in 5-HTT (s- vs l-alleles). *Source:* Adapted from Caspi et al. (2003).

a greater response in the neurobiology created by low MAOA conditions and hence in behavior. A similar case can be made in Figure 24.14: the effect of maltreatment on depression is dependent on the interaction of stress with different neurobiological trait levels created by genetic variation in 5-HTT (s- vs l-alleles).

Finally, these various considerations can be modeled more formally as in Figure 24.15, where the risk of lying within the reaction surface of personality disturbance is a function of three variables. First, extremity of the trait values of neurobiological variables underlying a critical subset of emotional traits (such as a combination of high neuroticism and social rejection sensitivity, and low affiliative reward) is on the horizontal axis. Again, this

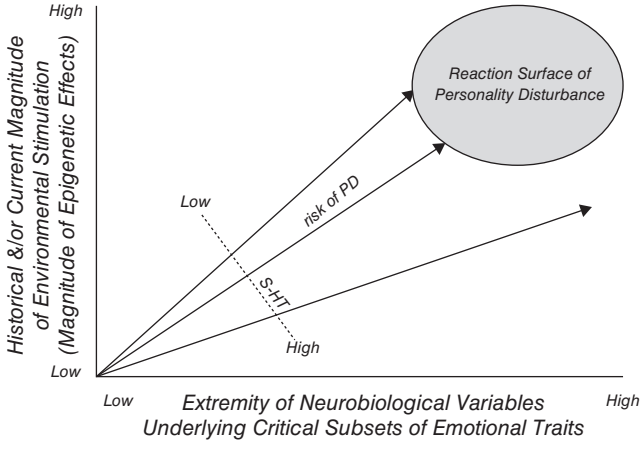


Figure 24.15 Nature of the interaction between environmental and neurobiological variables in the development of personality disturbance.

serves as the foundation of risk, the sine qua non for the development of personality disturbance. This foundation is set by genetic factors (but of course later reflects a history of gene–environment interaction), which may have their greatest impact on neural development during critical early life periods up to adolescence. Second, an individual's magnitude of historical or current environmental stress is a substantial contributor to development of personality disturbance. But as shown in the figure, the environmental effect varies in its magnitude as a function of neurobiological trait levels on the horizontal axis. This implies that the magnitude of epigenetic effects is dependent on neurobiological trait levels, being greatest at extreme neurobiological levels. At low neurobiological trait levels, environmental impact via epigenetic effects are hypothesized, as illustrated in Figures 24.6 (bottom row), 24.12, 24.13, and 24.14, to be limited. Lastly, level of 5-HT functioning is expected to modify risk for lying within the reaction surface of personality disturbance, particularly by its effect on neurobiological reactivity to stimulus provocation (i.e., the magnitude of epigenetic effects induced by environmental provocation). *Reduced* 5-HT functioning is hypothesized to (1) enhance the reactivity of neurobiological variables to stress, thereby (2) increasing enduring epigenetic effects and thus extremity of trait neurobiological functioning of variables on the horizontal axis, and (3) risk of lying within the reaction surface for personality disturbance, where reduced intensities of environmental stress are required to induce epigenetic effects in the neurobiological variables on the horizontal axis—an effect represented by elevation of the upper diagonal in the figure. Thus, in this model of personality disturbance, both genetic and environmental factors play key roles, the relative influence of which probably varies as a function of type of genes, cumulative environments, developmental period, and behavioral patterns.

Translational Implications

The stated goal of translational research, particularly as advocated by the National Institute of Mental Health (National Advisory Mental Health Council, 2000), is twofold. First, in both the childhood and adult psychopathology domains, the explicit goal of developmental and experimental psychopathology research is the illumination of those factors responsible for the pathophysiology of mental illness. The second aspect of the goal—the translational element—is the explicit interest in the translation of behavioral science and neuroscience research discoveries into innovations in the clinical care for those suffering from the many forms of psychopathology. Given that what we have termed *personality disturbance* (more typically termed *personality disorder*) affects approximately 10% of the population (Lenzenweger, 2008), the public health implications of this type of psychopathology for the population are clearly quite striking. Personality disturbance is well-known to be associated with considerable direct-care costs and after-care costs as well as foregone earnings that are appreciable. Moreover, personality disturbance causes considerable impacts not only on the person who suffers from a form of personality disorder but also relations with family members, friends, and coworkers. Finally, personality disturbance in parents will likely impact their ability to provide an optimal environment for the psychological and psychosocial development of their children, thus representing a factor that will enhance risk of disorder in the children (in addition, obviously, to the contributions made toward pathology via genetic and epigenetic inputs from the same parents). Thus, the translational emphasis in relation to personality disturbance is extraordinarily relevant as we move forward in our understanding of the basic mechanisms and processes involved in the etiology and development of personality disturbance. In our model we have sought to articulate the manner in which basic neurobehavioral systems, impacted by environmental factors, can create a matrix from which personality disturbance can arise as an emergent product. However, this model is not only useful as a theoretical exercise and a heuristic for research, but rather the primary neurobehavioral systems we have identified (incentive motivation/agentic extraversion; social closeness/affiliative extraversion; anxiety; fear; neural constraint) all represent targets for the development of treatments. Each of these primary neurobehavioral systems could easily be the focus for the development of novel psychopharmacological interventions (cf. Nunes, Carroll, & Bickel, 2002). The implications of our model, moreover, extend beyond the development of pharmacological interventions for personality disturbance in the translational paradigm, but they also strike us as consistent with the development of psychotherapy strategies that might impact the psychological and social processes we discuss (Tashiro & Mortensen, 2006). For example, further refinement of psychotherapeutic strategies explicitly directed at enhancing constraint, facilitating social closeness, altering cognitions related to the meaning of rewards (or accessibility of reward), or moderating anxiety, fear, and rejection sensitivity strike us as viable and, more importantly, substantively guided translational efforts.

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